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(54) Title: NOVEL COMPOUNDS

(57) Abstract: Polypeptides and polynucleotides of the genes set forth in Table I and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing polypeptides and polynucleotides of the genes set forth in Table I in diagnostic assays.

Novel Compounds

Field of Invention

This invention relates to newly identified polypeptides and polynucleotides encoding such polypeptides, to their use in diagnosis and in identifying compounds that may be agonists, antagonists that are potentially useful in therapy, and to production of such polypeptides and polynucleotides. The polynucleotides and polypeptides of the present invention also relate to proteins with signal sequences which allow them to be secreted extracellularly or membrane-associated (hereinafter often referred collectively as secreted proteins or secreted polypeptides).

Background of the Invention

The drug discovery process is currently undergoing a fundamental revolution as it embraces "functional genomics", that is, high throughput genome- or gene-based biology. This approach as a means to identify genes and gene products as therapeutic targets is rapidly superseding earlier approaches based on "positional cloning". A phenotype, that is a biological function or genetic disease, would be identified and this would then be tracked back to the responsible gene, based on its genetic map position.

Functional genomics relies heavily on high-throughput DNA sequencing technologies and the various tools of bioinformatics to identify gene sequences of potential interest from the many molecular biology databases now available. There is a continuing need to identify and characterise further genes and their related polypeptides/proteins, as targets for drug discovery.

Proteins and polypeptides that are naturally secreted into blood, lymph and other body fluids, or secreted into the cellular membrane are of primary interest for pharmaceutical research and development. The reason for this interest is the relative ease to target protein therapeutics into their place of action (body fluids or the cellular membrane). The natural pathway for protein secretion into extracellular space is the endoplasmic reticulum in eukaryotes and the inner membrane in prokaryotes (Palade, 1975, Science, 189, 347; Milstein, Brownlee, Harrison, and Mathews, 1972, Nature New Biol., 239, 117; Blobel, and Dobberstein, 1975, J. Cell. Biol., 67, 835). On the other hand, there is no known natural pathway for exporting a protein from the exterior of the cells into the cytosol (with the exception of pinocytosis, a mechanism of snake venom toxin intrusion into cells). Therefore targeting protein therapeutics into cells poses extreme difficulties.

The secreted and membrane-associated proteins include but are not limited to all peptide hormones and their receptors (including but not limited to insulin, growth hormones, chemokines, cytokines, neuropeptides, integrins, kallikreins, lamins, melanins, natriuretic hormones, neuropsin, neurotropins, pituitiary hormones, pleiotropins,

prostaglandins, secretogranins, selectins, thromboglobulins, thymosins), the breast and colon cancer gene products, leptin, the obesity gene protein and its receptors, serum albumin, superoxide dismutase, spliceosome proteins, 7TM (transmembrane) proteins also called as G-protein coupled receptors, immunoglobulins, several families of serine proteinases (including but not limited to proteins of the blood coagulation cascade, digestive enzymes), deoxyribonuclease I, etc.

Therapeutics based on secreted or membrane-associated proteins approved by FDA or foreign agencies include but are not limited to insulin, glucagon, growth hormone, chorionic gonadotropin, follicle stimulating hormone, luteinizing hormone, calcitonin, adrenocorticotropic hormone (ACTH), vasopressin, interleukines, interferones, immunoglobulins, lactoferrin (diverse products marketed by several companies), tissue-type plasminogen activator (Alteplase by Genentech), hyaulorindase (Wydase by Wyeth-Ayerst), dornase alpha (Pulmozyme\ by Genentech), Chymodiactin (chymopapain by Knoll), alglucerase (Ceredase by Genzyme), streptokinase (Kabikinase by Pharmacia) (Streptase by Astra), etc. This indicates that secreted and membrane-associated proteins have an established, proven history as therapeutic targets. Clearly, there is a need for identification and characterization of further secreted and membrane-associated proteins which can play a role in preventing, ameliorating or correcting dysfunction or disease, including but not limited to diabetes, breast-, prostate-, colon cancer and other malignant tumors, hyper- and hypotension, obesity, bulimia, anorexia, growth abnormalities, asthma, manic depression, dementia, delirium, mental retardation, Huntington's disease, Tourette's syndrome, schizophrenia, growth, mental or sexual development disorders, and dysfunctions of the blood cascade system including those leading to stroke. The proteins of the present invention which include the signal sequences are also useful to further elucidate the mechanism of protein transport which at present is not entirely understood, and thus can be used as research tools.

Summary of the Invention

The present invention relates to particular polypeptides and polynucleotides of the genes set forth in Table I, including recombinant materials and methods for their production. Such polypeptides and polynucleotides are of interest in relation to methods of treatment of certain diseases, including, but not limited to, the diseases set forth in Tables III and V, hereinafter referred to as "diseases of the invention". In a further aspect, the invention relates to methods for identifying agonists and antagonists (*e.g.*, inhibitors) using the materials provided by the invention, and treating conditions associated with imbalance of polypeptides and/or polynucleotides of the genes set forth in Table I with the identified compounds. In still a further aspect, the invention

relates to diagnostic assays for detecting diseases associated with inappropriate activity or levels the genes set forth in Table I. Another aspect of the invention concerns a polynucleotide comprising any of the nucleotide sequences set forth in the Sequence Listing and a polypeptide comprising a polypeptide encoded by the nucleotide sequence. In another aspect, the invention relates to a polypeptide comprising any of the polypeptide sequences set forth in the Sequence Listing and recombinant materials and methods for their production. Another aspect of the invention relates to methods for using such polypeptides and polynucleotides. Such uses include the treatment of diseases, abnormalities and disorders (hereinafter simply referred to as diseases) caused by abnormal expression, production, function and or metabolism of the genes of this invention, and such diseases are readily apparent by those skilled in the art from the homology to other proteins disclosed for each attached sequence. In still another aspect, the invention relates to methods to identify agonists and antagonists using the materials provided by the invention, and treating conditions associated with the imbalance with the identified compounds. Yet another aspect of the invention relates to diagnostic assays for detecting diseases associated with inappropriate activity or levels of the secreted proteins of the present invention.

Description of the Invention

In a first aspect, the present invention relates to polypeptides the genes set forth in Table I. Such polypeptides include:

(a) an isolated polypeptide encoded by a polynucleotide comprising a sequence set forth in the Sequence Listing, herein when referring to polynucleotides or polypeptides of the Sequence Listing, a reference is also made to the Sequence Listing referred to in the Sequence Listing;

(b) an isolated polypeptide comprising a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(c) an isolated polypeptide comprising a polypeptide sequence set forth in the Sequence Listing;

(d) an isolated polypeptide having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(e) a polypeptide sequence set forth in the Sequence Listing; and

(f) an isolated polypeptide having or comprising a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polypeptide sequence set forth in the Sequence Listing;

(g) fragments and variants of such polypeptides in (a) to (f).

Polypeptides of the present invention are believed to be members of the gene families set forth in Table II . They are therefore of therapeutic and diagnostic interest for the reasons set forth in Tables III and V. The biological properties of the polypeptides and polynucleotides of the genes

set forth in Table I are hereinafter referred to as "the biological activity" of polypeptides and polynucleotides of the genes set forth in Table I. Preferably, a polypeptide of the present invention exhibits at least one biological activity of the genes set forth in Table I.

Polypeptides of the present invention also include variants of the aforementioned polypeptides, including all allelic forms and splice variants. Such polypeptides vary from the reference polypeptide by insertions, deletions, and substitutions that may be conservative or non-conservative, or any combination thereof. Particularly preferred variants are those in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acids are inserted, substituted, or deleted, in any combination.

Preferred fragments of polypeptides of the present invention include an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids from an amino acid sequence set forth in the Sequence Listing, or an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids truncated or deleted from an amino acid sequence set forth in the Sequence Listing. Preferred fragments are biologically active fragments that mediate the biological activity of polypeptides and polynucleotides of the genes set forth in Table I, including those with a similar activity or an improved activity, or with a decreased undesirable activity. Also preferred are those fragments that are antigenic or immunogenic in an animal, especially in a human.

Fragments of a polypeptide of the invention may be employed for producing the corresponding full-length polypeptide by peptide synthesis; therefore, these variants may be employed as intermediates for producing the full-length polypeptides of the invention. A polypeptide of the present invention may be in the form of the "mature" protein or may be a part of a larger protein such as a precursor or a fusion protein. It is often advantageous to include an additional amino acid sequence that contains secretory or leader sequences, pro-sequences, sequences that aid in purification, for instance multiple histidine residues, or an additional sequence for stability during recombinant production.

Polypeptides of the present invention can be prepared in any suitable manner, for instance by isolation form naturally occurring sources, from genetically engineered host cells comprising expression systems (*vide infra*) or by chemical synthesis, using for instance automated peptide synthesizers, or a combination of such methods. Means for preparing such polypeptides are well understood in the art.

In a further aspect, the present invention relates to polynucleotides of the genes set forth in Table I. Such polynucleotides include:

(a) an isolated polynucleotide comprising a polynucleotide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polynucleotide sequence set forth in the Sequence Listing;

(b) an isolated polynucleotide comprising a polynucleotide set forth in the Sequence Listing;

(c) an isolated polynucleotide having at least 95%, 96%, 97%, 98%, or 99% identity to a polynucleotide set forth in the Sequence Listing;

(d) an isolated polynucleotide set forth in the Sequence Listing;

(e) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(f) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide set forth in the Sequence Listing;

(g) an isolated polynucleotide having a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(h) an isolated polynucleotide encoding a polypeptide set forth in the Sequence Listing;

(i) an isolated polynucleotide having or comprising a polynucleotide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polynucleotide sequence set forth in the Sequence Listing;

(j) an isolated polynucleotide having or comprising a polynucleotide sequence encoding a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polypeptide sequence set forth in the Sequence Listing; and

polynucleotides that are fragments and variants of the above mentioned polynucleotides or that are complementary to above mentioned polynucleotides, over the entire length thereof.

Preferred fragments of polynucleotides of the present invention include an isolated polynucleotide comprising an nucleotide sequence having at least 15, 30, 50 or 100 contiguous nucleotides from a sequence set forth in the Sequence Listing, or an isolated polynucleotide comprising a sequence having at least 30, 50 or 100 contiguous nucleotides truncated or deleted from a sequence set forth in the Sequence Listing.

Preferred variants of polynucleotides of the present invention include splice variants, allelic variants, and polymorphisms, including polynucleotides having one or more single nucleotide polymorphisms (SNPs).

Polynucleotides of the present invention also include polynucleotides encoding polypeptide variants that comprise an amino acid sequence set forth in the Sequence Listing and in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acid residues are substituted, deleted or added, in any combination.

In a further aspect, the present invention provides polynucleotides that are RNA transcripts of the DNA sequences of the present invention. Accordingly, there is provided an RNA polynucleotide that:

(a) comprises an RNA transcript of the DNA sequence encoding a polypeptide set forth in the Sequence Listing;

(b) is a RNA transcript of a DNA sequence encoding a polypeptide set forth in the Sequence Listing;

(c) comprises an RNA transcript of a DNA sequence set forth in the Sequence Listing; or

(d) is a RNA transcript of a DNA sequence set forth in the Sequence Listing;

and RNA polynucleotides that are complementary thereto.

The polynucleotide sequences set forth in the Sequence Listing show homology with the polynucleotide sequences set forth in Table II. A polynucleotide sequence set forth in the Sequence Listing is a cDNA sequence that encodes a polypeptide set forth in the Sequence Listing. A polynucleotide sequence encoding a polypeptide set forth in the Sequence Listing may be identical to a polypeptide encoding a sequence set forth in the Sequence Listing or it may be a sequence other than a sequence set forth in the Sequence Listing, which, as a result of the redundancy (degeneracy) of the genetic code, also encodes a polypeptide set forth in the Sequence Listing. A polypeptide of a sequence set forth in the Sequence Listingis related to other proteins of the gene families set forth in Table II, having homology and/or structural similarity with the polypeptides set forth in Table II. Preferred polypeptides and polynucleotides of the present invention are expected to have, *inter alia*, similar biological functions/properties to their homologous polypeptides and polynucleotides. Furthermore, preferred polypeptides and polynucleotides of the present invention have at least one activity of the genes set forth in Table I.

Polynucleotides of the present invention may be obtained using standard cloning and screening techniques from a cDNA library derived from mRNA from the tissues set forth in Table IV (see for instance, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). Polynucleotides of the invention can also be obtained from natural sources such as genomic DNA libraries or can be synthesized using well known and commercially available techniques.

When polynucleotides of the present invention are used for the recombinant production of polypeptides of the present invention, the polynucleotide may include the coding sequence for the mature polypeptide, by itself, or the coding sequence for the mature polypeptide in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence, or other fusion peptide portions. For example, a marker sequence that facilitates purification of the fused polypeptide can be encoded. In certain preferred embodiments

of this aspect of the invention, the marker sequence is a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, Proc Natl Acad Sci USA (1989) 86:821-824, or is an HA tag. A polynucleotide may also contain non-coding 5' and 3' sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

Polynucleotides that are identical, or have sufficient identity to a polynucleotide sequence set forth in the Sequence Listing, may be used as hybridization probes for cDNA and genomic DNA or as primers for a nucleic acid amplification reaction (for instance, PCR). Such probes and primers may be used to isolate full-length cDNAs and genomic clones encoding polypeptides of the present invention and to isolate cDNA and genomic clones of other genes (including genes encoding paralogs from human sources and orthologs and paralogs from species other than) that have a high sequence similarity to sequences set forth in the Sequence Listing, typically at least 95% identity. Preferred probes and primers will generally comprise at least 15 nucleotides, preferably, at least 30 nucleotides and may have at least 50, if not at least 100 nucleotides. Particularly preferred probes will have between 30 and 50 nucleotides. Particularly preferred primers will have between 20 and 25 nucleotides.

A polynucleotide encoding a polypeptide of the present invention, including homologs from species other than , may be obtained by a process comprising the steps of screening a library under stringent hybridization conditions with a labeled probe having a sequence set forth in the Sequence Listing or a fragment thereof, preferably of at least 15 nucleotides; and isolating full-length cDNA and genomic clones containing the polynucleotide sequence set forth in the Sequence Listing. Such hybridization techniques are well known to the skilled artisan. Preferred stringent hybridization conditions include overnight incubation at 42°C in a solution comprising: 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10 % dextran sulfate, and 20 microgram/ml denatured, sheared salmon sperm DNA; followed by washing the filters in 0.1x SSC at about 65°C. Thus the present invention also includes isolated polynucleotides, preferably with a nucleotide sequence of at least 100, obtained by screening a library under stringent hybridization conditions with a labeled probe having the sequence set forth in the Sequence Listing or a fragment thereof, preferably of at least 15 nucleotides.

The skilled artisan will appreciate that, in many cases, an isolated cDNA sequence will be incomplete, in that the region coding for the polypeptide does not extend all the way through to the 5' terminus. This is a consequence of reverse transcriptase, an enzyme with inherently low "processivity" (a measure of the ability of the enzyme to remain attached to the template during the

polymerisation reaction), failing to complete a DNA copy of the mRNA template during first strand cDNA synthesis.

There are several methods available and well known to those skilled in the art to obtain full-length cDNAs, or extend short cDNAs, for example those based on the method of Rapid Amplification of cDNA ends (RACE) (see, for example, Frohman et al., Proc Nat Acad Sci USA 85, 8998-9002, 1988). Recent modifications of the technique, exemplified by the Marathon (trade mark) technology (Clontech Laboratories Inc.) for example, have significantly simplified the search for longer cDNAs. In the Marathon (trade mark) technology, cDNAs have been prepared from mRNA extracted from a chosen tissue and an 'adaptor' sequence ligated onto each end. Nucleic acid amplification (PCR) is then carried out to amplify the "missing" 5' end of the cDNA using a combination of gene specific and adaptor specific oligonucleotide primers. The PCR reaction is then repeated using 'nested' primers, that is, primers designed to anneal within the amplified product (typically an adapter specific primer that anneals further 3' in the adaptor sequence and a gene specific primer that anneals further 5' in the known gene sequence). The products of this reaction can then be analyzed by DNA sequencing and a full-length cDNA constructed either by joining the product directly to the existing cDNA to give a complete sequence, or carrying out a separate full-length PCR using the new sequence information for the design of the 5' primer.

Recombinant polypeptides of the present invention may be prepared by processes well known in the art from genetically engineered host cells comprising expression systems. Accordingly, in a further aspect, the present invention relates to expression systems comprising a polynucleotide or polynucleotides of the present invention, to host cells which are genetically engineered with such expression systems and to the production of polypeptides of the invention by recombinant techniques. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention.

For recombinant production, host cells can be genetically engineered to incorporate expression systems or portions thereof for polynucleotides of the present invention. Polynucleotides may be introduced into host cells by methods described in many standard laboratory manuals, such as Davis et al., Basic Methods in Molecular Biology (1986) and Sambrook *et al.*(*ibid*). Preferred methods of introducing polynucleotides into host cells include, for instance, calcium phosphate transfection, DEAE-dextran mediated transfection, transvection, micro-injection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction or infection.

Representative examples of appropriate hosts include bacterial cells, such as *Streptococci*, *Staphylococci*, *E. coli*, *Streptomyces* and *Bacillus subtilis* cells; fungal cells, such as yeast cells and

Aspergillus cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, HEK 293 and Bowes melanoma cells; and plant cells.

A great variety of expression systems can be used, for instance, chromosomal, episomal and virus-derived systems, *e.g.*, vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements, such as cosmids and phagemids. The expression systems may contain control regions that regulate as well as engender expression. Generally, any system or vector that is able to maintain, propagate or express a polynucleotide to produce a polypeptide in a host may be used. The appropriate polynucleotide sequence may be inserted into an expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth in Sambrook *et al.*, (*ibid*). Appropriate secretion signals may be incorporated into the desired polypeptide to allow secretion of the translated protein into the lumen of the endoplasmic reticulum, the periplasmic space or the extracellular environment. These signals may be endogenous to the polypeptide or they may be heterologous signals.

If a polypeptide of the present invention is to be expressed for use in screening assays, it is generally preferred that the polypeptide be produced at the surface of the cell. In this event, the cells may be harvested prior to use in the screening assay. If the polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide. If produced intracellularly, the cells must first be lysed before the polypeptide is recovered.

Polypeptides of the present invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well known techniques for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during intracellular synthesis, isolation and/or purification.

Polynucleotides of the present invention may be used as diagnostic reagents, through detecting mutations in the associated gene. Detection of a mutated form of a gene is characterized by the polynucleotides set forth in the Sequence Listing in the cDNA or genomic sequence and which is associated with a dysfunction. Will provide a diagnostic tool that can add to, or define, a diagnosis of a disease, or susceptibility to a disease, which results from under-expression, over-

expression or altered spatial or temporal expression of the gene. Individuals carrying mutations in the gene may be detected at the DNA level by a variety of techniques well known in the art.

Nucleic acids for diagnosis may be obtained from a subject's cells, such as from blood, urine, saliva, tissue biopsy or autopsy material. The genomic DNA may be used directly for detection or it may be amplified enzymatically by using PCR, preferably RT-PCR, or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeled nucleotide sequences of the genes set forth in Table I. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence difference may also be detected by alterations in the electrophoretic mobility of DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing (see, for instance, Myers *et al.*, Science (1985) 230:1242). Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method (see Cotton *et al.*, Proc Natl Acad Sci USA (1985) 85: 4397-4401).

An array of oligonucleotides probes comprising polynucleotide sequences or fragments thereof of the genes set forth in Table I can be constructed to conduct efficient screening of *e.g.*, genetic mutations. Such arrays are preferably high density arrays or grids. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability, see, for example, M. Chee et al., Science, 274, 610-613 (1996) and other references cited therein. Detection of abnormally decreased or increased levels of polypeptide or mRNA expression may also be used for diagnosing or determining susceptibility of a subject to a disease of the invention. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the art for the quantitation of polynucleotides, such as, for example, nucleic acid amplification, for instance PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such as a polypeptide of the present invention, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radio-immunoassays, competitive-binding assays, Western Blot analysis and ELISA assays.

Thus in another aspect, the present invention relates to a diagnostic kit comprising:
(a) a polynucleotide of the present invention, preferably the nucleotide sequence set forth in the Sequence Listing , or a fragment or an RNA transcript thereof;
(b) a nucleotide sequence complementary to that of (a);

(c) a polypeptide of the present invention, preferably the polypeptide set forth in the Sequence Listing or a fragment thereof; or

(d) an antibody to a polypeptide of the present invention, preferably to the polypeptide set forth in the Sequence Listing .

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component. Such a kit will be of use in diagnosing a disease or susceptibility to a disease, particularly diseases of the invention, amongst others.

The polynucleotide sequences of the present invention are valuable for chromosome localisation studies. The sequences set forth in the Sequence Listing are specifically targeted to, and can hybridize with, a particular location on an individual human chromosome. The mapping of relevant sequences to chromosomes according to the present invention is an important first step in correlating those sequences with gene associated disease. Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found in, for example, V. McKusick, Mendelian Inheritance in Man (available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region are then identified through linkage analysis (co-inheritance of physically adjacent genes). Precise human chromosomal localisations for a genomic sequence (gene fragment etc.) can be determined using Radiation Hybrid (RH) Mapping (Walter, M. Spillett, D., Thomas, P., Weissenbach, J., and Goodfellow, P., (1994) A method for constructing radiation hybrid maps of whole genomes, Nature Genetics 7, 22-28). A number of RH panels are available from Research Genetics (Huntsville, AL, USA) e.g. the GeneBridge4 RH panel (Hum Mol Genet 1996 Mar;5(3):339-46 A radiation hybrid map of the human genome. Gyapay G, Schmitt K, Fizames C, Jones H, Vega-Czarny N, Spillett D, Muselet D, Prud'Homme JF, Dib C, Auffray C, Morissette J, Weissenbach J, Goodfellow PN). To determine the chromosomal location of a gene using this panel, 93 PCRs are performed using primers designed from the gene of interest on RH DNAs. Each of these DNAs contains random human genomic fragments maintained in a hamster background (human / hamster hybrid cell lines). These PCRs result in 93 scores indicating the presence or absence of the PCR product of the gene of interest. These scores are compared with scores created using PCR products from genomic sequences of known location. This comparison is conducted at http://www.genome.wi.mit.edu/.

The polynucleotide sequences of the present invention are also valuable tools for tissue expression studies. Such studies allow the determination of expression patterns of polynucleotides of the present invention which may give an indication as to the expression patterns of the encoded polypeptides in tissues, by detecting the mRNAs that encode them. The techniques used are well

known in the art and include in situ hydridization techniques to clones arrayed on a grid, such as cDNA microarray hybridization (Schena *et al*, Science, 270, 467-470, 1995 and Shalon *et al*, Genome Res, 6, 639-645, 1996) and nucleotide amplification techniques such as PCR. A preferred method uses the TAQMAN (Trade mark) technology available from Perkin Elmer. Results from these studies can provide an indication of the normal function of the polypeptide in the organism. In addition, comparative studies of the normal expression pattern of mRNAs with that of mRNAs encoded by an alternative form of the same gene (for example, one having an alteration in polypeptide coding potential or a regulatory mutation) can provide valuable insights into the role of the polypeptides of the present invention, or that of inappropriate expression thereof in disease. Such inappropriate expression may be of a temporal, spatial or simply quantitative nature.

A further aspect of the present invention relates to antibodies. The polypeptides of the invention or their fragments, or cells expressing them, can be used as immunogens to produce antibodies that are immunospecific for polypeptides of the present invention. The term "immunospecific" means that the antibodies have substantially greater affinity for the polypeptides of the invention than their affinity for other related polypeptides in the prior art.

Antibodies generated against polypeptides of the present invention may be obtained by administering the polypeptides or epitope-bearing fragments, or cells to an animal, preferably a non-human animal, using routine protocols. For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler, G. and Milstein, C., Nature (1975) 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.*, Immunology Today (1983) 4:72) and the EBV-hybridoma technique (Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, 77-96, Alan R. Liss, Inc., 1985).

Techniques for the production of single chain antibodies, such as those described in U.S. Patent No. 4,946,778, can also be adapted to produce single chain antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms, including other mammals, may be used to express humanized antibodies.

The above-described antibodies may be employed to isolate or to identify clones expressing the polypeptide or to purify the polypeptides by affinity chromatography. Antibodies against polypeptides of the present invention may also be employed to treat diseases of the invention, amongst others.

Polypeptides and polynucleotides of the present invention may also be used as vaccines. Accordingly, in a further aspect, the present invention relates to a method for inducing an immunological response in a mammal that comprises inoculating the mammal with a polypeptide of the present invention, adequate to produce antibody and/or T cell immune response, including,

for example, cytokine-producing T cells or cytotoxic T cells, to protect said animal from disease, whether that disease is already established within the individual or not. An immunological response in a mammal may also be induced by a method comprises delivering a polypeptide of the present invention *via* a vector directing expression of the polynucleotide and coding for the polypeptide *in vivo* in order to induce such an immunological response to produce antibody to protect said animal from diseases of the invention. One way of administering the vector is by accelerating it into the desired cells as a coating on particles or otherwise. Such nucleic acid vector may comprise DNA, RNA, a modified nucleic acid, or a DNA/RNA hybrid. For use a vaccine, a polypeptide or a nucleic acid vector will be normally provided as a vaccine formulation (composition). The formulation may further comprise a suitable carrier. Since a polypeptide may be broken down in the stomach, it is preferably administered parenterally (for instance, subcutaneous, intra-muscular, intravenous, or intra-dermal injection). Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats and solutes that render the formulation instonic with the blood of the recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in water systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

Polypeptides of the present invention have one or more biological functions that are of relevance in one or more disease states, in particular the diseases of the invention hereinbefore mentioned. It is therefore useful to identify compounds that stimulate or inhibit the function or level of the polypeptide. Accordingly, in a further aspect, the present invention provides for a method of screening compounds to identify those that stimulate or inhibit the function or level of the polypeptide. Such methods identify agonists or antagonists that may be employed for therapeutic and prophylactic purposes for such diseases of the invention as hereinbefore mentioned. Compounds may be identified from a variety of sources, for example, cells, cell-free preparations, chemical libraries, collections of chemical compounds, and natural product mixtures. Such agonists or antagonists so-identified may be natural or modified substrates, ligands, receptors, enzymes, etc., as the case may be, of the polypeptide; a structural or functional mimetic thereof (see Coligan *et al.*, Current Protocols in Immunology 1(2):Chapter 5 (1991)) or a small molecule. Such small molecules preferably have a molecular weight below 2,000 daltons, more

preferably between 300 and 1,000 daltons, and most preferably between 400 and 700 daltons. It is preferred that these small molecules are organic molecules.

The screening method may simply measure the binding of a candidate compound to the polypeptide, or to cells or membranes bearing the polypeptide, or a fusion protein thereof, by means of a label directly or indirectly associated with the candidate compound. Alternatively, the screening method may involve measuring or detecting (qualitatively or quantitatively) the competitive binding of a candidate compound to the polypeptide against a labeled competitor (*e.g.* agonist or antagonist). Further, these screening methods may test whether the candidate compound results in a signal generated by activation or inhibition of the polypeptide, using detection systems appropriate to the cells bearing the polypeptide. Inhibitors of activation are generally assayed in the presence of a known agonist and the effect on activation by the agonist by the presence of the candidate compound is observed. Further, the screening methods may simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide of the present invention, to form a mixture, measuring an activity of the genes set forth in Table I in the mixture, and comparing activity of the mixture of the genes set forth in Table I to a control mixture which contains no candidate compound.

Polypeptides of the present invention may be employed in conventional low capacity screening methods and also in high-throughput screening (HTS) formats. Such HTS formats include not only the well-established use of 96- and, more recently, 384-well micotiter plates but also emerging methods such as the nanowell method described by Schullek et al, Anal Biochem., 246, 20-29, (1997).

Fusion proteins, such as those made from Fc portion and polypeptide of the genes set forth in Table I, as hereinbefore described, can also be used for high-throughput screening assays to identify antagonists for the polypeptide of the present invention (see D. Bennett *et al.*, J Mol Recognition, 8:52-58 (1995); and K. Johanson *et al.*, J Biol Chem, 270(16):9459-9471 (1995)).

The polynucleotides, polypeptides and antibodies to the polypeptide of the present invention may also be used to configure screening methods for detecting the effect of added compounds on the production of mRNA and polypeptide in cells. For example, an ELISA assay may be constructed for measuring secreted or cell associated levels of polypeptide using monoclonal and polyclonal antibodies by standard methods known in the art. This can be used to discover agents that may inhibit or enhance the production of polypeptide (also called antagonist or agonist, respectively) from suitably manipulated cells or tissues.

A polypeptide of the present invention may be used to identify membrane bound or soluble receptors, if any, through standard receptor binding techniques known in the art. These include, but are not limited to, ligand binding and crosslinking assays in which the polypeptide is

labeled with a radioactive isotope (for instance, ^{125}I), chemically modified (for instance, biotinylated), or fused to a peptide sequence suitable for detection or purification, and incubated with a source of the putative receptor (cells, cell membranes, cell supernatants, tissue extracts, bodily fluids). Other methods include biophysical techniques such as surface plasmon resonance and spectroscopy. These screening methods may also be used to identify agonists and antagonists of the polypeptide that compete with the binding of the polypeptide to its receptors, if any. Standard methods for conducting such assays are well understood in the art.

Examples of antagonists of polypeptides of the present invention include antibodies or, in some cases, oligonucleotides or proteins that are closely related to the ligands, substrates, receptors, enzymes, etc., as the case may be, of the polypeptide, *e.g.*, a fragment of the ligands, substrates, receptors, enzymes, etc.; or a small molecule that bind to the polypeptide of the present invention but do not elicit a response, so that the activity of the polypeptide is prevented.

Screening methods may also involve the use of transgenic technology and the genes set forth in Table I. The art of constructing transgenic animals is well established. For example, the genes set forth in Table I may be introduced through microinjection into the male pronucleus of fertilized oocytes, retroviral transfer into pre- or post-implantation embryos, or injection of genetically modified, such as by electroporation, embryonic stem cells into host blastocysts. Particularly useful transgenic animals are so-called "knock-in" animals in which an animal gene is replaced by the human equivalent within the genome of that animal. Knock-in transgenic animals are useful in the drug discovery process, for target validation, where the compound is specific for the human target. Other useful transgenic animals are so-called "knock-out" animals in which the expression of the animal ortholog of a polypeptide of the present invention and encoded by an endogenous DNA sequence in a cell is partially or completely annulled. The gene knock-out may be targeted to specific cells or tissues, may occur only in certain cells or tissues as a consequence of the limitations of the technology, or may occur in all, or substantially all, cells in the animal. Transgenic animal technology also offers a whole animal expression-cloning system in which introduced genes are expressed to give large amounts of polypeptides of the present invention

Screening kits for use in the above described methods form a further aspect of the present invention. Such screening kits comprise:

(a) a polypeptide of the present invention;

(b) a recombinant cell expressing a polypeptide of the present invention;

(c) a cell membrane expressing a polypeptide of the present invention; or

(d) an antibody to a polypeptide of the present invention;

which polypeptide is preferably that set forth in the Sequence Listing.

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component.

Glossary

The following definitions are provided to facilitate understanding of certain terms used frequently hereinbefore.

"Antibodies" as used herein includes polyclonal and monoclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, including the products of an Fab or other immunoglobulin expression library.

"Isolated" means altered "by the hand of man" from its natural state, *i.e.*, if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living organism is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein. Moreover, a polynucleotide or polypeptide that is introduced into an organism by transformation, genetic manipulation or by any other recombinant method is "isolated" even if it is still present in said organism, which organism may be living or non-living.

"Secreted protein activity or secreted polypeptide activity" or "biological activity of the secreted protein or secreted polypeptide" refers to the metabolic or physiologic function of said secreted protein including similar activities or improved activities or these activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said secreted protein.

"Secreted protein gene" refers to a polynucleotide comprising any of the attached nucleotide sequences or allelic variants thereof and/or their complements.

"Polynucleotide" generally refers to any polyribonucleotide (RNA) or polydeoxribonucleotide (DNA), which may be unmodified or modified RNA or DNA. "Polynucleotides" include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term "polynucleotide" also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications may be made to DNA and RNA; thus,

"polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

"Polypeptide" refers to any polypeptide comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. "Polypeptide" refers to both short chains, commonly referred to as peptides, oligopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. "Polypeptides" include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques that are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications may occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present to the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from post-translation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, biotinylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination (see, for instance, Proteins - Structure and Molecular Properties, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993; Wold, F., Post-translational Protein Modifications: Perspectives and Prospects, 1-12, in Post-translational Covalent Modification of Proteins, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter *et al.*, "Analysis for protein modifications and nonprotein cofactors", Meth Enzymol, 182, 626-646, 1990, and Rattan *et al.*, "Protein Synthesis: Post-translational Modifications and Aging", Ann NY Acad Sci, 663, 48-62, 1992).

"Fragment" of a polypeptide sequence refers to a polypeptide sequence that is shorter than the reference sequence but that retains essentially the same biological function or activity as the

reference polypeptide. "Fragment" of a polynucleotide sequence refers to a polynucleotide sequence that is shorter than the reference sequence set forth in the Sequence Listing.

"Variant" refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide, but retains the essential properties thereof. A typical variant of a polynucleotide differs in nucleotide sequence from the reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from the reference polypeptide. Generally, alterations are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, insertions, deletions in any combination. A substituted or inserted amino acid residue may or may not be one encoded by the genetic code. Typical conservative substitutions include Gly, Ala; Val, Ile, Leu; Asp, Glu; Asn, Gln; Ser, Thr; Lys, Arg; and Phe and Tyr. A variant of a polynucleotide or polypeptide may be naturally occurring such as an allele, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis. Also included as variants are polypeptides having one or more post-translational modifications, for instance glycosylation, phosphorylation, methylation, ADP ribosylation and the like. Embodiments include methylation of the N-terminal amino acid, phosphorylations of serines and threonines and modification of C-terminal glycines.

"Allele" refers to one of two or more alternative forms of a gene occurring at a given locus in the genome.

"Polymorphism" refers to a variation in nucleotide sequence (and encoded polypeptide sequence, if relevant) at a given position in the genome within a population.

"Single Nucleotide Polymorphism" (SNP) refers to the occurrence of nucleotide variability at a single nucleotide position in the genome, within a population. An SNP may occur within a gene or within intergenic regions of the genome. SNPs can be assayed using Allele Specific Amplification (ASA). For the process at least 3 primers are required. A common primer is used in reverse complement to the polymorphism being assayed. This common primer can be between 50 and 1500 bps from the polymorphic base. The other two (or more) primers are identical to each other except that the final 3' base wobbles to match one of the two (or more) alleles that make up the polymorphism. Two (or more) PCR reactions are then conducted on sample DNA, each using the common primer and one of the Allele Specific Primers.

"Splice Variant" as used herein refers to cDNA molecules produced from RNA molecules initially transcribed from the same genomic DNA sequence but which have undergone alternative RNA splicing. Alternative RNA splicing occurs when a primary RNA transcript undergoes splicing, generally for the removal of introns, which results in the production of more than one mRNA molecule each of that may encode different amino acid sequences. The term splice variant also refers to the proteins encoded by the above cDNA molecules.

"Identity" reflects a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, determined by comparing the sequences. In general, identity refers to an exact nucleotide to nucleotide or amino acid to amino acid correspondence of the two polynucleotide or two polypeptide sequences, respectively, over the length of the sequences being compared.

"% Identity" - For sequences where there is not an exact correspondence, a "% identity" may be determined. In general, the two sequences to be compared are aligned to give a maximum correlation between the sequences. This may include inserting "gaps" in either one or both sequences, to enhance the degree of alignment. A % identity may be determined over the whole length of each of the sequences being compared (so-called global alignment), that is particularly suitable for sequences of the same or very similar length, or over shorter, defined lengths (so-called local alignment), that is more suitable for sequences of unequal length.

"Similarity" is a further, more sophisticated measure of the relationship between two polypeptide sequences. In general, "similarity" means a comparison between the amino acids of two polypeptide chains, on a residue by residue basis, taking into account not only exact correspondences between a between pairs of residues, one from each of the sequences being compared (as for identity) but also, where there is not an exact correspondence, whether, on an evolutionary basis, one residue is a likely substitute for the other. This likelihood has an associated "score" from which the "% similarity" of the two sequences can then be determined.

Methods for comparing the identity and similarity of two or more sequences are well known in the art. Thus for instance, programs available in the Wisconsin Sequence Analysis Package, version 9.1 (Devereux J et al, Nucleic Acids Res, 12, 387-395, 1984, available from Genetics Computer Group, Madison, Wisconsin, USA), for example the programs BESTFIT and GAP, may be used to determine the % identity between two polynucleotides and the % identity and the % similarity between two polypeptide sequences. BESTFIT uses the "local homology" algorithm of Smith and Waterman (J Mol Biol, 147,195-197, 1981, Advances in Applied Mathematics, 2, 482-489, 1981) and finds the best single region of similarity between two sequences. BESTFIT is more suited to comparing two polynucleotide or two polypeptide sequences that are dissimilar in length, the program assuming that the shorter sequence represents

a portion of the longer. In comparison, GAP aligns two sequences, finding a "maximum similarity", according to the algorithm of Neddleman and Wunsch (J Mol Biol, 48, 443-453, 1970). GAP is more suited to comparing sequences that are approximately the same length and an alignment is expected over the entire length. Preferably, the parameters "Gap Weight" and "Length Weight" used in each program are 50 and 3, for polynucleotide sequences and 12 and 4 for polypeptide sequences, respectively. Preferably, % identities and similarities are determined when the two sequences being compared are optimally aligned.

Other programs for determining identity and/or similarity between sequences are also known in the art, for instance the BLAST family of programs (Altschul S F et al, J Mol Biol, 215, 403-410, 1990, Altschul S F et al, Nucleic Acids Res., 25:389-3402, 1997, available from the National Center for Biotechnology Information (NCBI), Bethesda, Maryland, USA and accessible through the home page of the NCBI at www.ncbi.nlm.nih.gov) and FASTA (Pearson W R, Methods in Enzymology, 183, 63-99, 1990; Pearson W R and Lipman D J, Proc Nat Acad Sci USA, 85, 2444-2448,1988, available as part of the Wisconsin Sequence Analysis Package).

Preferably, the BLOSUM62 amino acid substitution matrix (Henikoff S and Henikoff J G, Proc. Nat. Acad Sci. USA, 89, 10915-10919, 1992) is used in polypeptide sequence comparisons including where nucleotide sequences are first translated into amino acid sequences before comparison.

Preferably, the program BESTFIT is used to determine the % identity of a query polynucleotide or a polypeptide sequence with respect to a reference polynucleotide or a polypeptide sequence, the query and the reference sequence being optimally aligned and the parameters of the program set at the default value, as hereinbefore described.

"Identity Index" is a measure of sequence relatedness which may be used to compare a candidate sequence (polynucleotide or polypeptide) and a reference sequence. Thus, for instance, a candidate polynucleotide sequence having, for example, an Identity Index of 0.95 compared to a reference polynucleotide sequence is identical to the reference sequence except that the candidate polynucleotide sequence may include on average up to five differences per each 100 nucleotides of the reference sequence. Such differences are selected from the group consisting of at least one nucleotide deletion, substitution, including transition and transversion, or insertion. These differences may occur at the 5' or 3' terminal positions of the reference polynucleotide sequence or anywhere between these terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. In other words, to obtain a polynucleotide sequence having an Identity Index of 0.95 compared to a reference polynucleotide sequence, an average of up to 5 in every 100 of the nucleotides of the in the reference sequence may be deleted, substituted or inserted, or any combination thereof, as

hereinbefore described. The same applies *mutatis mutandis* for other values of the Identity Index, for instance 0.96, 0.97, 0.98 and 0.99.

Similarly, for a polypeptide, a candidate polypeptide sequence having, for example, an Identity Index of 0.95 compared to a reference polypeptide sequence is identical to the reference sequence except that the polypeptide sequence may include an average of up to five differences per each 100 amino acids of the reference sequence. Such differences are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion. These differences may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between these terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. In other words, to obtain a polypeptide sequence having an Identity Index of 0.95 compared to a reference polypeptide sequence, an average of up to 5 in every 100 of the amino acids in the reference sequence may be deleted, substituted or inserted, or any combination thereof, as hereinbefore described. The same applies *mutatis mutandis* for other values of the Identity Index, for instance 0.96, 0.97, 0.98 and 0.99.

The relationship between the number of nucleotide or amino acid differences and the Identity Index may be expressed in the following equation:

$$n_a \leq x_a - (x_a \bullet I),$$

in which:

n_a is the number of nucleotide or amino acid differences,

x_a is the total number of nucleotides or amino acids in a sequence set forth in the Sequence Listing,

I is the Identity Index,

• is the symbol for the multiplication operator, and

in which any non-integer product of x_a and I is rounded down to the nearest integer prior to subtracting it from x_a.

"Homolog" is a generic term used in the art to indicate a polynucleotide or polypeptide sequence possessing a high degree of sequence relatedness to a reference sequence. Such relatedness may be quantified by determining the degree of identity and/or similarity between the two sequences as hereinbefore defined. Falling within this generic term are the terms "ortholog", and "paralog". "Ortholog" refers to a polynucleotide or polypeptide that is the functional equivalent of the polynucleotide or polypeptide in another species. "Paralog" refers to a polynucleotideor polypeptide that within the same species which is functionally similar.

"Fusion protein" refers to a protein encoded by two, often unrelated, fused genes or fragments thereof. In one example, EP-A-0 464 533-A discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, employing an immunoglobulin Fc region as a part of a fusion protein is advantageous for use in therapy and diagnosis resulting in, for example, improved pharmacokinetic properties [see, *e.g.*, EP-A 0232 262]. On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

Table I.

Gene Name	GSK Gene ID	Nucleic Acid SEQ ID NO's	Corresponding Protein SEQ ID NO's
sbgTango79a	14898	SEQ ID NO:1	SEQ ID NO:24
sbgPRO331a	14908	SEQ ID NO:2	SEQ ID NO:25
sbghPYYa	24835	SEQ ID NO:3	SEQ ID NO:26
sbghGTa	25306	SEQ ID NO:4	SEQ ID NO:27
SB-HDGF	42748	SEQ ID NO:5 SEQ ID NO:6	SEQ ID NO:28 SEQ ID NO:29
SBhACRP30a	34718	SEQ ID NO:7 SEQ ID NO:8	SEQ ID NO:30 SEQ ID NO:31
sbg35069DBIa	35069	SEQ ID NO:9	SEQ ID NO:32
sbg14862SPERCTa	14862	SEQ ID NO:10 SEQ ID NO:11	SEQ ID NO:33 SEQ ID NO:34
sbg24878SIa	24878	SEQ ID NO:12 SEQ ID NO:13	SEQ ID NO:35 SEQ ID NO:36
sbg34976IGBa	34976	SEQ ID NO:14	SEQ ID NO:37
sbg41608HDGFa	41608	SEQ ID NO:15	SEQ ID NO:38
sbg66804SPARCra	66804	SEQ ID NO:16 SEQ ID NO:17	SEQ ID NO:39 SEQ ID NO:40
sbg72825FOLATEa	72825	SEQ ID NO:18	SEQ ID NO:41
SBhPRO221	73255	SEQ ID NO:19	SEQ ID NO:42
sbg77153CYSa	77153	SEQ ID NO:20	SEQ ID NO:43
SBh80014.IAPa	80014	SEQ ID NO:21 SEQ ID NO:22	SEQ ID NO:44 SEQ ID NO:45
sbgFGF-19b	68602	SEQ ID NO:23	SEQ ID NO:46

Table II

Gene Name	Gene Family	Closest Polynuclotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbgTango79a	Slit-like membrane glycoprotein	GB:AC004152 Joint Genome Institute, Lawrence Livermore National Laboratory, 7000 East Ave., Livermore, CA 94551, USA	The human Tango-79 protein, geneseqp:W84596 Patent number and publication date: WO9906427-A1 11-Feb-99	membrane-bound
sbgPRO331a	Slit-like membrane glycoprotein	GB:AC008039 Human Genome Center, University of Washington, Box 352145, Seattle, WA 98195, USA	The human protein PRO331, geneseqp:Y13394 Patent number and publication date: WO9914328-A2 25-Mar-99	membrane-bound
sbghPYYa	Peptide YY	GB:AJ239323	Human peptideYY,	secreted

		Max-Planck-Institute for Molecular Genetics	gi:1172796 Kohri,K., Nata,K., Yonekura,H., Nagai, A., Konno,K. and Okamoto,H. Biochim. Biophys. Acta 1173 (3), 345-349 (1993)	
sbghGTa	Gonadotropin beta chain	GB:AL049871 Genoscope – Centre National de Sequencage :BP 19191006 EVRY cedex FRANCE	Pacific herring gonadotropin II-beta,gi:4200297 Power,M.E., Carolsfield,J, Wallis, G.P. and Sherwood, N.M. J. Fish Biol. 50, 315-323 (1997)	secreted
SB-HDGF	Hepatoma derived growth factor (HDGF)	JGI:CIT978SKB_50L17 Found at Joint Genome Institute	Mouse HDGF, gi: 2558501 Biochem. Biophys. Res. Commun. 238(1), 26-32, 1997	secreted
SBhACRP30a	Complement C1q/TNF	GB:AC007016 Submitted (08-May-99) by Department of Genetics, Stanford Human Genome Center, 855 Miranda Avenue, Palo, CA 94304	Mouse30 Kda adipocyte complement-related protein ACRP30, gi: 1051268 P. Sherer et al., J.Biol. Chem. 270(18), 10697-10703, 1996.	secreted
sbg35069DBIa	Neuropeptide	EMBL:AC010999 Submitted (29-Sep-1999) by Multimegabase Sequencing Center, University of Washington, P.O. Box 357730. Seattle, WA 98195	ACYL-COA-BINDING PROTEIN HOMOLOG (ACBP), gi:1168274 Lihrmann, I. et al. Proc. Natl. Acad. Sci. U.S.A. 91 (15), 6899-6903 (1994)	cytosolic
sbg14862SPERCTa	speract receptor	GB:AC005522 (WU:H_DJ1129E2) submitted by Genome Sequencing Center, Washington University, School of Medicine, 4444 Forest Park Parkway, St. Lous, MO 63108, USA	gp-340, a putative opsonin receptor for lung surfactant, gi:5733598 Holmskov U, Mollenhauer J, Madsen J, Vitved L, Gronlund J, Tornoe I, Kliem A, Reid KB, Poustka A, Skjodt K, Proc Natl Acad Sci U S A 1999 Sep 14; 96(19):10794-9.	membrane-bound
sbg24878SIa	laminin type EGF, EGF2, ldlra2, dlra2, ldlra1 and EGF1	SC:AL109804 found at Sanger Center	Mouse sialoadhesin gene, gi:2769747 Mucklow S, Gordon S, Crocker PR. Mamm Genome 1997 Dec;8(12):934-7	secreted
sbg34976IGBa	Slit-like membrane glycoprotein	GB:AC010931 Submitted (30-JAN-1999) by Genome Sequencing Center, Washington University	Immunoglobulin superfamily containing leucine-rich repeat, gi:5031809 Nagasawa A, Kubota R,	membrane-bound

		School of Medicine, 4444 Forest Park Parkway, St. Louis, MO 63108, USA	Imamura Y, Nagamine K, Wang Y, Asakawa S, Kudoh J, Minoshima S, Mashima Y, Oguchi Y, Shimizu N, Genomics 1997 Sep 15;44(3):273-9	
sbg41608HDGFa	Hepatoma-derived growth factor	GB:AL033539 Submitted by Sanger Center Hinxton, Cambridgeshire, CB10 1SA, UK	Bovine hepatoma-derived growth factor, gi:945419 Biochem. Biophys. Res. Commun. 238(1):26-32, 1997	secreted
sbg66804SPARCra	Sparc-related protein	GB:AL135747 Submitted by Genoscope – Centre National de Sequencage :BP 19191006 EVRY cedex, FRANCE	Mouse SPARC-related rpotein, gi:5305327 Submitted (05-Jun-1998) by GeneCraft, Treskowst. 10, Muenster 48163, Germany.	membrane-bound
sbg72825FOLATEa	Folate receptor	SB:AP000765 Submitted (25-NOV-1999) by Masahira Hattori, The Institute of Physical and ChemicalResearch (RIKEN), Genomic Sciences Center (GSC); 1-7-22 Suehiro-chou, Tsurumi-ku,Yokohama, Kanagawa 230-0045, Japan	Sus scrofa membrance-bound folate binding protein, gi:4928859 Vallet,J.L., Smith,T.P.L., Sontegard,T., Pearson,P.L.,Christenson, R.K. and Klemcke,H.G. Biol. Reprod. 61(2):372 (1999)	membrane-bound
SBhPRO221	Slit-like membrane glycoprotein	GB:AP001065 Submitted (12-JAN-2000) by Nobuyoshi Shimizu, Keio University, School of Medicine, Molecular Biology; 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan	New isolated human gene, geneseqp:Y13356. WO9914328-A2, Chen, J. Goddard, A., Yuan, J., Genentech Inc. 25th June 1999 GPS	membrane-bound
sbg77153CYSa	Testatin	GB:AL121894 Submitted by Sanger Center	Mouse testatin precursor, gi:3928491 Tohonen,V., Osterlund,C. and Nordqvist,K. Proc. Natl. Acad. Sci. U.S.A. 95 (24), 14208-14213 (1998).	secreted
SBh80014.IAPa	Inhibitor of apoptosis protein (IAP)	GB:AL121827 Submitted by Sanger Center	human putative inhibitor of apoptosis, gi: 3914339 C. Stehlik et al, Biochem. Biophys. Res. Commun. 243(3), 827-832, 1998	cytosolic

sbgFGF-19b	Fibroblast Growth Factor	GB:AB018122Homo sapiens mRNA for FGF-19, complete cds (Nishimura,T., Utsunomiya,Y., Hoshikawa,M., Ohuchi,H. and Itoh,N. Structure and expression of a novel human FGF, FGF-19, expressed in the fetal brain. Biochim. Biophys. Acta 1444 (1), 148-151 (1999))	FGF-19 (gi 5668601, gi 4826726, gi4514718, (Nishimura,T., Utsunomiya,Y., Hoshikawa,M., Ohuchi,H. and Itoh,N. Structure and expression of a novel human FGF, FGF-19, expressed in the fetal brain. Biochim. Biophys. Acta 1444 (1), 148-151 (1999))	secreted

Table III.

Gene Name	Uses	Associated Diseases
sbgTango79a	An embodiment of the invention is the use of sbgTango79a, a secreted protein, in the diagnosis and treatment of Tango-associated diseases and involvement in gastrointestinal ulceration. Close Homologs of sbgTango79a are Tango 79 and PRO227.	Alzheimers disease, ALS, abnormal keratinocyte differentiation, anti thrombosis, atrophia areata, cell growth, congenital microvillus atrophy, dermal scarring, enterocolitis, cancer, gastrointestinal ulceration, neuropathy, Parkinson's disease, psoriasis, skin diseases, Usher's syndrome, wound healing, and Zollinger-Ellison syndrome
sbgPRO331a	An embodiment of the invention is the use of sbgPRO331a, in the treatment of gastrointestinal ulceration and involved in nutritional activity, cytokine and cell proliferation/differentiation activity, immune stimulating (e.g. as vaccines) or suppressing activity, haematopoiesis regulating activity, tissue growth activity, activin/inhibin activity, chemotactic/chemokinetic activity, haemostatic and thrombolytic activity, receptor/ligand activity, anti-inflammatory activity, cadherin/tumour invasion suppressor activity, and tumour inhibition activity. The polynucleotides of sbgPRO331a may also be useful for gene therapy. Close Homologs of sbgPRO331a are PRO331 and AS209_1.	Alzheimers disease, ALS, abnormal keratinocyte differentiation, anti-thrombosis, atrophia areata, cell growth, hematopoietic disease, diseases of the immune system, inflammation, congenital microvillus atrophy, dermal scarring, enterocolitis, cancer, gastrointestinal ulceration, neuropathy, Parkinson's disease, psoriasis, skin diseases, Usher's syndrome, wound healing, and Zollinger-Ellison syndrome
sbghPYYa	An embodiment of the invention is the use of sbghPYYa, to identify new receptors and receptor agonists, antagonists, or protein agents. A close homolog of sbghPYYa is Peptide YY precursor, a clinically significant member of the neuropeptide family which include peptides such as pancreatic hormone, neuropeptide Y (NPY) and peptide YY (PYY). These neuropeptides are ligands for G-protein coupled receptors.	Anxiety, schizophrenia, feeding disorders, anorexia, depression, grooming, stretching, yawning, social, sexual and rewarded behavior, chronic and acute inflammation, cardiovasuclar disease, sleep disorder, learning and memory alteration and altered immune response, cancer, seizure, stroke, migraine, asthma, neuropathy and aging
sbghGTa	Human gonadotropin most similar to luteinizing hormone, sbghGTa, is exploitable in similar ways to luteinizing hormone or its releasing hormone. Luteinizing hormone is helpful in ovulation induction for reproductive procedures (Fertil. Steril.	Sexual disorders, infertility, blocking fertility, hypogonadism, prostate and other cancers, treatment of transsexuals

	1999. 71(3):405-414). Luteinizing hormone-releasing hormone and its agonists are exploited to reduce androgen levels in prostate cancer (Oncology. 1998. 12(4):499-505). Gonadotropin releasing hormone use is helpful in polycystic ovary syndrome (Eur. J. Contracept. Reprod.Health Care. 1997. 2(4):213-224).	
SB-HDGF	An embodiment of the invention is the use of SB-HDGF, to control cell growth and regulation of cell differentiation. Hepatoma-derived growth factors are members of a diverse family of cytokines. Like other cytokines, they are peptides involved in the control of cell growth regulation, differentiation and function(Thomson, The Cytokine Handbook, 2nd edition, Academic Press, Harcourt Brace & co. publishers, London). Another embodiment of the invention is the use of SB-HDGF for diagnosis or therapeutic treatment of human hepatoma. HDGFs are structurally related to Fibroblast growth factors (Klagsbrun M., Sasse, J., Proc. Natl.Acad. Sci. USA 1986 83(8) 2448-52). This putative growth factor may play an important role in autonomous growth of hepatoma and may lead to useful diagnosis or therapeutic approaches to Human Hepatoma (Nakamura, H., Kambe,H., Egawa, T Clin Chim Acta 1989, 183(3):273-84). A further embodiment of the invention is the use of SB-HDGF to prevent tumor growth. Inhibition of fibroblast growth factor-2 by the compound Suramin prevents neovascularisation and tumor growth in mice (Pesenti et al., British Journal of Cancer, 66:367-372.)	Cancer, inflammation, defective immune response, cardiovadcular disease, growth abnormalities
SBhACRP30a	Based on EST expression data, SBHACRP30a is primarily or exclusively expressed in heart. Based on the similiarity of SBHACRP30a to ACRP30, Hib27, C1q complement proteins, TNF, and other members of the TNF superfamily, an embodiment of the invention is the use that the encoded protein of SBhACRP30a may play a role in inflammation, cell proliferation, cell death, immunity, and/or energy homeostatis processes. SBHACRP30a show highest similarity to one member of this superfamily, ACRP30 (Adipocyte Complement-Related Protein of 30 kDa). ACRP30 is made exclusively in adipocytes, and its expression is dysregulated in various forms of obesity (Hu, E, Liang, P and Spiegelman, BM. J. Biol. Chem 271, 10697-10703, 1996). ACRP30 secretion is acutely stimulated by insulin (Scherer, PE, Williams S., Fogliano, M., Baldini, G. and Lodish, J Biol. Chem. 270, 26746-26749, 1995) and is repressed by chronically elevated levels of insulin. A related molecule, the Hib27 protein from Siberian chipmunks, seems also to be involved in energy homeostasis, as its expression is specifically extinguished during hibernation (Takamatsu, N., Ohba, K., Kondo, J.,Kondo, N., and Shiba, T. Mol. Cell Biol.13 1516-1521, 1993). Recently, it has been shown that the three dimensional structure of ACRP30 is superimposible with that of the TNF's, suggesting	Cancer, obesity, anorexia, inflammation , cardiovadcular disease, growth abnormalities

	that these proteins may have a similar function and mode of action (Shapiro, L and Scherer PE.,. Current Biology 8, 335-338, 1997). TNF's are known to play a role in energy homeostasis, where they are implicated in cachexia, obesity and in insulin resistance (Hotamisligil GS., and Spiegelman BM. Diabetes (1994) 43, 1271-1278; Teoman Uysal K., Wiesbrock SM, Marina MW and Hotamisligil GS, Nature 389, 610-614, 1997).	
sbg35069DBIa	An embodiment of the invention is the use of sbg35069DBIa to function as a neuropeptide, modulating the activity of the GABA receptor. A simular homologue can displace diazepam from benzodiazepine (BZD) recognition site on GABA type A receptors. As such, it may function as a neuropeptide, modulating the activity of the GABA receptor (J.B.C. 1986. 261(21):9727-31). Two forms, short and long (Biochem. J. 1995. 306:327-30), are predicted to be intracellular and secreted, respectively.	Anxiety, schizophrenia, feeding disorders, anorexia, depression, grooming, stretching, yawning, social, sexual and rewarded behavior, chronic and acute inflammation, cardiovasuclar disease, sleep disorder, learning and memory alteration and altered immune response, cancer, seizure, stroke, migraine, asthma, neuropathy and aging
sbg14862SPERCTa	An embodiment of the invention is the use of sbg14862SPERCTa, a secreted protein, in the diagnosis and treatment of cancers. A close homolog of sbg14862SPERCTa is human secreted protein SRCR.	Cancer, infections, autoimmune diseases, wound healing and hematopoietic disorder
sbg24878SIa	An embodiment of the invention is the use that the encoded protein of sbg24878SIa, a member of the immunoglobulin superfamily, may play a roll in cell-cell interactions. The closest homologue to this protein is the mouse sialoadhesin genes, a macrophage sialic acid binding receptor for haemopoietic cells with 17 immunoglobulin-like domains, is proposed to function in both secreted and membrane-bound forms and involved in cell-cell interactions. A further embodiment of the invention is the use of sbg24878SIa to inhibit T-cell-B-cell interactions for treating auto-immune disease such as rheumatoid arthritis, systemic lupus erythematosus etc. Close Homologs of sbg24878SIa are mouse sialoadhesin genes and CD22 beta.	Auto-immune diseases such as rheumatoid arthritis, systemic lupus erythematosus and tumors
sbg34976IGBa	An embodiment of the invention is the use of sbg34976IGBa, a secreted protein, in the diagnosis and treatment of Bardet-Biedl syndrome type 4 (BBS4). A close homolog of sbg34976IGBa is leucine rich repeat (ISLR) mRNA.	Alzheimers disease, ALS, abnormal keratinocyte differentiation, anti-thrombosis, atrophia areata, cell growth, hematopoietic disease, diseases of the immune system, inflammation, congenital microvillus atrophy, dermal scarring, enterocolitis, cancer, gastrointestinal ulceration, neuropathy, Parkinson's disease, psoriasis, skin diseases, Usher's syndrome, wound healing, and Zollinger-Ellison syndrome
sbg41608HDGFa	An embodiment of the invention is the use of sbg41608HDGFa, to control cell growth and regulation of cell differentiation. Hepatoma-derived growth factors are members of a diverse family of cytokines. Like other cytokines, they are peptides involved in the control of cell growth, regulation,	Cancer, inflammation, defective immune response, cardiovascular disease, growth abnormalities

	differentiation and function (e.g. Thomson, The Cytokine Handbook, 2nd edition, Academic Press, Harcourt Brace & co. publishers, London). Another embodiment of the invention is the use of sbg41608HDGFa for diagnosis or therapeutic treatment of human hepatoma. HDGF are structurally related to Fibroblast growth factors (Klagsbrun M., Sasse, J., Proc. Natl.Acad. Sci. USA 1986 83(8) 2448-52). This putative growth factor may play an important role in autonomous growth of hepatoma and may lead to useful diagnosis or therapeutic approaches to Human Hepatoma (Nakamura, H., Kambe, H., Egawa, T Clin Chim Acta 1989, 183(3):273-84,). A further embodiment of the invention is the use of sbg41608HDGFa to prevent tumor growth. Inhibition of fibroblast growth factor-2 by the compound Suramin prevents neovascularisation and tumor growth in mice (Pesenti et al., British Journal of Cancer, 66:367-372)	
sbg66804SPARCra	An embodiment of the invention is the use of sbg66804SPARCra, in development, remodeling, cell turnover, tissue repair, and tumor growth. The closest homologue to this secreted protein is the mouse SPARC-related protein. SPARC (Secreted Protein, Acidic and Rich in Cysteine) is a unique matricellular glycoprotein that is expressed by many different types of cells and is associated with development, remodeling, cell turnover, and tissue repair. Its principal functions in vitro are counteradhesion and antiproliferation, which proceed via different signaling pathways. SPARC has demonstrated activities in angiogenesis, cataractogenesis, and wound healing. SPARC has also been identified in tumors.	Cataractogenesis, angiogenesis, wound healing, tumors
sbg72825FOLATEa	An embodiment of the invention is the use of sbg72825FOLATEa in the diagnostic and treatment applications of malignant, such as epithelial cancers, ovary, uterus, cervix cancer and future cancer vaccine developments. A close homolog of sbg72825FOLATEa is membrane bound folate binding protein.	Epithelial cancers, ovary, uterus and cervix cancer
SBhPRO221	An embodiment of the invention is the use of SBhPRO221 in disorders associated with preservation and maintenance of gastric mucosa, treatment of chronic and acute gastric ulcer, skin disease like epithelial cancer, lung squamous carcinoma, neuropathy, Parkinson disease, Alzheimer disease, tissue repair, problems of kidney, endometrium, blood vessels and other tissue in genital tract.	Disorders associated with healthy maintanance of gastric mucosa and repair of acute and chronic mucosal lesion, skin disease, lung carcinoma, growth abnormalities, Parkinson, Alzheimer's dosaes, ALS, neuropathy and cancer
sbg77153CYSa	An embodiment of the invention is the use of sbg77153CYSa in natural tissue remodeling events such as bone resorption and embryo implantation along with associations with tumor formation and metastasis. The closest homologue is the mouse testatin precursor (Cystatin 9), is related to a group of genes that encodes cysteine protease inhibitors known as cystatins. Cystatins and their target	Tumors and matastasis, remodeling bone resorption and embryo implantation

	proteases have been associated with tumor formation and metastasis, but also are involved in natural tissue remodeling events such as bone resorption and embryo implantation.	
SBh80014.IAPa	An embodiment of the invention is the use of SBh80014.IAPa in inhibition of apoptosos and thus in, cell proliferation, cancer, metastasis, cell death, immunity, and energy homeostatis processes. A close homolog to SBh80014.IAPa is PIAP(putative inhibitor of apoptosis protein) (C. Stehlik et al, Biochem. Biophys. Res. Commun. 243(3), 827-832, 1998). PIAP is made primarlily in tumor cells and is strongly upregulated in response to inflammatory cytokine TNF-•, IL-1 and lipopolysacchrides. The members of this family are conserved across species.	Suppression of apoptosis, cell proliferation, cancer, metastasis, Inflammation, defective immune response, growth abnormalities
sbgFGF-19b	An embodiment of the invention is the use of sbgFGF-19b in cell growth, regulation, differentiation, function, angiogenesis, neovascularisation, wound healing, astrogliosis, glial cell proliferation and differentiation, cerebral vasodilation, neurotrophic/neuromodulatory processes, improves the outcome in cerebral ischemia, promotes neoangiogenesis in ischemic myocardium, and enhances functional recovery and/or promotes neuronal sprouting following focal cerebral infarct. Fibroblast growth factors are a diverse family of cytokines. Like other cytokines, they are peptides involved in the control of cell growth, regulation, differentiation and function (e.g. Thomson, The Cytokine Handbook, 2nd edition, Academic Press, Harcourt Brace & co. publishers, London). Fibroblast growth factors are so called because they are fibroblast mitogens (Gospodarawicz, Journal of Biological Chemistry, (1975) 250: 2515-2520,). Inhibition of fibroblast growth factor-2 by the compound Suramin prevents neovascularisation and tumor growth in mice (Pesenti et al., British Journal of Cancer, 66:367-372). Fibroblast growth factors also function in angiogenesis (Lyons, M.K., et al., Brain Res. (1991) 558:315-320), wound healing (Uhl, E., et al., Br. J. Surg. (1993) 80:977-980, 1993), astrogliosis, glial cell proliferation and differentiation (Biagini, G. et al., Neurochem. Int. (1994) 25:17-24), cerebral vasodilation (Tanaka, R. et al., Stroke (1995) 26:2154-2159), and neurotrophic/neuromodulatory processes. Fibroblast growth factor also has multiple positive effects including blood flow and protection from calcium toxicity to improve outcome in cerebral ischemia (Mattson, M.P. et al., Semin. Neurosci. (1993) 5:295-307; Doetrocj. W.D. et al., J. Neurotrauma (1996) 13:309-316). Basic FGF treatment promotes neoangiogenesis in ischemic myocardium (Schumacher et al., Circulation (1998) 97: 645-650). Basic FGF enhances functional recovery and promotes neuronal sprouting following focal cerebral infarct (Kawamata et al., Proc.Natl. Acad. Sci.(1997) 94 (15):8179-84).	Cerebral ischemia, cancer, atherosclerosis, rheumatoid arthritis, cirrhosis, psoriasis, sarcoidosis, idiopathic pulmonary fibrosis, tumor development, developmental disorders, skeletal disorders, wound repair

Table IV. Quantitative, Tissue-specific mRNA expression detected using SybrMan or TaqMan.

Quantitative, tissue-specific, mRNA expression patterns of the genes were measured using SYBR-Green Quantitative PCR (Applied Biosystems, Foster City, CA) or TaqMan PCR (Perkin Elmer, see Lie et al. Current Opinion in Biotechnology 9:43-48, 1998; Gibson et al., Genome Methods 6:995-1001, 1996) and human cDNAs prepared from various human tissues. Gene-specific PCR primers were designed using the first nucleic acid sequence listed in the Sequence List for each gene. Results are presented as the number of copies of each specific gene's mRNA detected in 1ng mRNA pool from each tissue. Two replicate mRNA measurements were made from each tissue RNA.

SybrMan Results:

Gene Name	Tissue-Specific mRNA Expression (copies per ng mRNA; avg. ± range for 2 data points per tissue)									
	Brain	Heart	Lung	Liver	Kidney	Skeletal muscle	Intestine	Spleen/ lymph	Placenta	Testis
sbgTango79a	358±7	278±55	239±100	53±20	247±29	461±60	83±1	202±18	300±55	770±106
sbgPRO331a	15411±861	1831±25	2409±103	656±2	2283±82	625±47	510±5	2096±74	2596±68	4692±472
sbghPYYa	-3±1	-1±0	0±0	-7±8	8±2	-5±9	-4±1	2±1	-1±0	38±5
sbghGTa	24±10	5±4	5±3	-4±8	2±1	-3±5	-1±3	4±2	4±0	92±8
SB-HDGF	4362±359	3387±11	2425±120	972±82	3270±152	7106±1647	1133±164	2058±101	2528±50	9024±652
SBhACRP30a	10751±954	7443±294	9900±780	6463±45	8530±225	7638±405	6040±438	8912±1021	8931±617	8098±612
sbg35069DBIa	142±15	180±17	94±10	37±3	257±15	73±8	27±10	76±29	184±5	158±2
sbg14862SPERCTa	31±3	18±6	23±4	10±6	49±1	8±7	7±0	23±1	18±2	30±1
sbg24878SIa	327±29	1251±8	1740±103	552±20	514±182	636±65	582±64	5200±222	5151±271	695±30
sbg34976IGBa	1500±64	451±21	123±14	9±6	55±6	156±6	38±12	80±4	76±3	1975±183
sbg41608HDGFa	11±4	3±0	4±4	2±0	0±1	1±2	1±0	7±5	0±0	14909±926
sbg66804SPARCra	296±53	24±0	4±1	457±21	7±0	68±3	9±1	439±11	128±1	1037±17
sbg72825FOLATEa	289±40	381±12	100±78	92±3	494±102	289±52	101±3	219±30	405±121	270±44
SBhPRO221	14±6	109±43	102±30	221±44	19±9	6±5	61±13	60±19	33±11	119±40
sbg77153CYSa	50±8	80±32	181±3	10±2	234±50	54±7	25±8	93±0	151±3	26223±604
SBh80014.IAPa	6±10	82±70	31±3	-2±3	110±1	88±24	17±4	29±1	62±3	65±20

Table IV (cont).

TaqMan Results:

Gene Name	Tissue-Specific mRNA Expression (copies per ng mRNA; avg. ± SD for 4 data points per tissue)									
	Brain	Heart	Lung	Liver	Kidney	Skeletal muscle	Intestine	Spleen	Placenta	Pancreas
sbgFGF-19b	9±9	25±30	8±11	1612+1711	9±16	10±9	9±15	16±20	0+3	123+144

Table V. Additional diseases based on mRNA expression in specific tissues

Tissue Expression	Additional Diseases
Brain	Neurological and psychiatric diseases, including Alzheimers, parasupranuclear palsey, Huntington's disease, myotonic dystrophy, anorexia, depression, schizophrenia, headache, amnesias, anxiety disorders, sleep disorders, multiple sclerosis
Heart	Cardiovascular diseases, including congestive heart failure, dilated cardiomyopathy, cardiac arrhythmias, Hodgson's Disease, myocardial infarction, cardiac arrhythmias
Lung	Respiratory diseases, including asthma, Chronic Obstructive Pulmonary Disease, cystic fibrosis, acute bronchitis, adult respiratory distress syndrome
Liver	Dyslipidemia, hypercholesterolemia, hypertriglyceridemia, cirrhosis, hepatic encephalopathy, fatty hepatocirrhosis, viral and nonviral hepatitis, Type II Diabetes Mellitis, impaired glucose tolerance
Kidney	Renal diseases, including acute and chronic renal failure, acute tubular necrosis, cystinuria, Fanconi's Syndrome, glomerulonephritis, renal cell carcinoma, renovascular hypertension
Skeletal muscle	Eulenburg's Disease, hypoglycemia, obesity, tendinitis, periodic paralyses, malignant hyperthermia, paramyotonia congenita, myotonia congenita
Intestine	Gastrointestinal diseases, including Myotonia congenita, Ileus, Intestinal Obstruction, Tropical Sprue, Pseudomembranous Enterocolitis
Spleen/lymph	Lymphangiectasia, hypersplenism, angiomas, ankylosing spondylitis, Hodgkin's Disease, macroglobulinemia, malignant lymphomas, rheumatoid arthritis
Placenta	Choriocarcinoma, hydatidiform mole, placenta previa
Testis	Testicular cancer, male reproductive diseases, including low testosterone and male infertility
Pancreas	Diabetic ketoacidosis, Type 1 & 2 diabetes, obesity, impaired glucose tolerance

What is claimed is:

1. An isolated polypeptide selected from the group consisting of:

(a) an isolated polypeptide encoded by a polynucleotide comprising a sequence set forth in Table I;

(b) an isolated polypeptide comprising a polypeptide sequence having at least 95% identity to a polypeptide sequence set forth in Table I;

(c) an isolated polypeptide comprising a polypeptide sequence set forth in Table I;

(d) an isolated polypeptide having at least 95% identity to a polypeptide sequence set forth in Table I;

(e) a polypeptide sequence of a gene set forth in Table I; and

(f) fragments and variants of such polypeptides in (a) to (e)

2. An isolated polynucleotide selected from the group consisting of:

(a) an isolated polynucleotide comprising a polynucleotide sequence having at least 95% identity to a polynucleotide sequence set forth in Table I;

(b) an isolated polynucleotide comprising a polynucleotide set forth in Table I;

(c) an isolated polynucleotide having at least 95% identity to a polynucleotide set forth in Table I;

(d) an isolated polynucleotide of a gene set forth in Table I;

(e) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide sequence having at least 95% identity to the polypeptide sequence set forth in Table I;

(f) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide set forth in Table I;

(g) an isolated polynucleotide having a polynucleotide sequence encoding a polypeptide sequence having at least 95% identity to a polypeptide sequence set forth in Table I;

(h) an isolated polynucleotide encoding a polypeptide set forth in Table I;

(i) an isolated polynucleotide with a nucleotide sequence of at least 100 nucleotides obtained by screening a library under stringent hybridization conditions with a labelled probe having a sequence set forth in Table I or a fragment thereof having at least 15 nucleotides;

(j) a polynucleotide which is an RNA equivalent of the polynucleotide of (a) to (i);

or a polynucleotide sequence complementary to said isolated polynucleotide

and polynucleotides that are variants and fragments of the above mentioned polynucleotides or that are complementary to above mentioned polynucleotides, over the entire length thereof.

3. An antibody immunospecific for the polypeptide of claim 1.

4. An antibody as claimed in claim 3 which is a polyclonal antibody.

5. An expression vector comprising a polynucleotide capable of producing a polypeptide of claim 1 when said expression vector is present in a compatible host cell.

6. A process for producing a recombinant host cell which comprises the step of introducing an expression vector comprising a polynucleotide capable of producing a polypeptide of claim 1 into a cell such that the host cell, under appropriate culture conditions, produces said polypeptide.

7. A recombinant host cell produced by the process of claim 6.

8. A membrane of a recombinant host cell of claim 7 expressing said polypeptide.

9. A process for producing a polypeptide which comprises culturing a host cell of claim 7 under conditions sufficient for the production of said polypeptide and recovering said polypeptide from the culture.

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<213> Homo sapiens

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<213> Homo sapiens

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atggcaggct ctgggccacc tctgcccacg tgcaatgcag aagtgggatg ggagaacatg 60
gctgaggacg gcaaggcttt tctaataagt gaccgtgacc cacagtgcaa cctccactgc 120
tccaggactc aacccaaacc catctgtgcc tctgatggca ggtcctacga gtccatgtgt 180
gagtaccagc gagccaagtg ccgagacccg accctgggcg tggtgcatcg aggtagatgc 240
aaagatgctg gccagagcaa gtgtcgcctg gagcgggctc aagccctgga gcaagccaag 300
aagcctcagg aagctgtgtt tgtcccagag tgtggcgagg atggctcctt tacccaggtg 360
cagtgccata cttacactgg gtactgctgg tgtgtcaccc cggatgggaa gcccatcagt 420
ggctcttctg tgcagaataa aactcctgta tgttcaggtt cagtcaccga caagcccttg 480
agccagggta actcaggaag gaaagatgac gggtctaagc cgacacccac gatggagacc 540
cagccggtgt tcgatggaga tgaaatcaca gccccaactc tatggattaa acacttggtg 600
atcaaggact ccaaactgaa caacaccaac ataagaaatt cagagaaagt ctattcgtgt 660
gaccaggaga ggcagagtgc cctggaagag gcccagcaga atccccgtga gggtattgtc 720
atccctgaat gtgcccctgg gggactctat aagccagtgc aatgccacca gtccactggc 780
tactgctggt gtgtgctggt ggacacaggg cgcccgctgc ctgggacctc cacacgctac 840
gtgatgccca gttgtgagag cgacgccagg gccaagacta cagaggcgga tgacccttc 900

aaggacaggg agctaccagg ctgtccagaa gggaagaaaa tggagtttat caccagccta 960
ctggatgctc tcaccactga catggttcag gccattaact cagcagcgcc cactggaggt 1020
gggaggttct cagagccaga ccccagccac accctggagg agcgggtagt gcactggtat 1080
ttcagccagc tggacagcaa tagcagcaac gacattaaca agcgggagat gaagcccttc 1140
aagcgctacg tgaagaagaa agccaagccc aagaaatgtg cccggcgttt caccgactac 1200
tgtgacctga acaaagacaa ggtcatttca ctgcctgagc tgaagggctg cctgggtgtt 1260
agcaaagaag gtggtagcct tggcagtttc ccccaggcaa aatga 1305

<210> 18
<211> 753
<212> DNA
<213> Homo sapiens

<400> 18
atggcatgct ggtggccgct cctgctagag ctgtggacag tcatgcccac ctgggctggg 60
gacgagctgc tcaacatctg catgaatgcc aaacaccaca agagagtgcc cagcccagaa 120
gacaagctct atgaggagtg catcccctgg aaggacaatg cctgctgcac cctcacgaca 180
agctgggaag cccatctgga tgtatcccca ctctacaact tcagcctgtt tcactgtgga 240
ctgctgatgc ctggctgtcg gaagcacttc atccaggcta tctgcttcta tgagtgctcc 300
ccaaacctgg ggccctggat ccagccagtg ggaagcctgg ggtgggaggt ggccccgagt 360
gggcagggag agcgagttgt gaatgtgccg ctgtgccagg aggactgtga ggagtggtgg 420
gaagactgtc gcatgtctta cacatgcaaa tccaactggc gtggtggctg ggactggagt 480
caggggaaga accgctgccc caaaggggcc cagtgcctcc ctttctccca ttacttcccc 540
accccagctg acctgtgtga gaagacttgg agcaattcct tcaaagccag ccctgagcga 600
cggaacagtg ggcggtgtct ccagaagtgg tttgagcctg ctcagggcaa ccccaatgtg 660
gccgtggccc gcctcttcgc cagctctgcc ccatcctggg aactgtccta caccatcatg 720
gtctgctccc tgttcctgcc gttcctttcc tga 753

<210> 19
<211> 774
<212> DNA
<213> Homo sapiens

<400> 19
atgggcaccg tgcgcccacc tcgcccctcg ctcctgctgg tctccacccg ggagtcttgt 60
ctcttcctcc tcttctgcct gcacctgggc gccgcctgcc cacagccctg ccggtgccct 120
gaccacgcag gggctgtggc tgtcttctgc agcttgcggg gccttcagga ggtccccgag 180
gacatcccgg ccaacaccgt gctcctgaag ctcgatgcca acaagatctc ccacctcccg 240
gacggggcct tccagcacct gcaccggctc agggagctgg atctgtctca caacgccatc 300
gaggccatcg gctccgccac cttcgcgggc ctggccgggg gcctgcggct gctggacctg 360
tcttacaacc gcatccagag gatccccaag gacgccctgg gcaaactcag cgccaagata 420
cgcctgtccc acaacccccct gcactgcgag tgcgccctgc aggaggccct gtgggagctg 480

aagctggacc ccgactctgt ggacgagatc gcctgccaca cctcagtgca ggaggagttt 540
gtggggaagc ctctggttca ggctctggat gcgggtgcca gcctctgcag cgtcccccac 600
aggaccacag acgtggccat gctggtcacc atgttcggct ggttcgccat ggtgatcgcc 660
tacgtcgtgt actatgtgcg ccacaaccag gaggatgccc ggaggcacct ggagtacctg 720
aagtctctgc ccagcgcccc cgcctccaag gaccccatcg gcccggggcc ctag 774

<210> 20
<211> 447
<212> DNA
<213> Homo sapiens

<400> 20
atgctgggcc tgccgtggaa gggaggtctg tcctgggcgc tgctgctgct tctcttaggc 60
tcccagatcc tgctgatcta tgcctggcat ttccacgagc aaagggactg tgatgaacac 120
aatgtcatgg ctcgttacct ccctgccaca gtggagtttg ctgtccacac attcaaccaa 180
cagagcaagg actactatgc ctacagactg gggcacatct tgaattcctg gaaggagcag 240
gtggagtcca agactgtatt ctcaatggag ctactgctgg ggagaactag gtgtgggaaa 300
tttgaagacg acattgacaa ctgccatttc caagaaagca cagagctgaa caatgtaaga 360
caggacacca gcttccctcc tggatacagc tgtggatgcc acatggggtg tggtgtgggc 420
acaggtgcaa ctgacaaaga gacttag 447

<210> 21
<211> 1068
<212> DNA
<213> Homo sapiens

<400> 21
atgggaccta aagacagtgc caagtgcctg caccgtggac cacagccgag ccactgggca 60
gccggtgatg gtcccacgca ggagcgctgt ggaccccgct ctctgggcag ccctgtccta 120
ggcctggaca cctgcagagc ctgggaccac gtggatgggc agatcctggg ccagctgcgg 180
cccctgacag aggaggaaga ggaggagggc gccggggcca ccttgtccag ggggcctgcc 240
ttccccggca tgggctctga ggagttgcgt ctggcctcct tctatgactg gccgctgact 300
gctgaggtgc cacccgagct gctggctgct gccggcttct tccacacagg ccatcaggac 360
aaggtgaggt gcttcttctg ctatgggggc ctgcagagct ggaagcgcgg ggacgacccc 420
tggacggagc atgccaagtg gttccccagc tgtcagttcc tgctccggtc aaaaggaaga 480
gactttgtcc acagtgtgca ggagactcac tcccagctgc tgggctcctg ggtgagcgcc 540
acctctcctc ggggctccgg gtggcagtgg ggtcctgccc ctcctatttc cccaaggcct 600
gatggtctct ggctccttcc aggacccgtg ggaagaaccg gaagacgcag cccctgtggc 660
cccctccggt ccagtctgaa agtgcccagg agccaggtgc aggcccggga ccccctgggt 720
gagggctggg gcaggggagg gctgagggac cccgaccttc catggcccat agagggtggg 780
ggccagggtg tggggacatt tcgcaggcct gtcctcctag gaggggtcag tccagccgag 840
gcccagaggg cgtggtgggt tcttgagccc ccaggagcca gggatgtgga ggcgcagctg 900

cggcggctgc aggaggagag gacgtgcaag gtgtgcctgg accgcgccgt gtccatcgtc 960
tttgtgccgt gcggccacct ggtctgtgct gagtgtgccc ccggcctgca gctgtgcccc 1020
atctgcagag cccccgtccg cagccgcgtg cgcaccttcc tgtcctag 1068

<210> 22
<211> 769
<212> DNA
<213> Homo sapiens

<400> 22
atgggaccta aagacagtgc caagtgcctg caccgtggac cacagccgag ccactgggca 60
gccggtgatg gtcccacgca ggagcgctgt ggaccccgct ctctgggcag ccctgtccta 120
ggcctggaca cctgcagagc ctgggaccac gtggatgggc agatcctggg ccagctgcgg 180
cccctgacag aggaggaaga ggaggagggc gccggggcca ccttgtccag ggggcctgcc 240
ttccccggca tgggctctga ggagttgcgt ctggcctcct tctatgactg gccgctgact 300
gctgaggtgc cacccgagct gctggctgct gccggcttct tccacacagg ccatcaggac 360
aaggtgaggt gcttcttctg ctatgggggc ctgcagagct ggaagcgcgg ggacgacccc 420
tggacggagc atgccaagtg gttccccctg tcagttcctg ctccggtcaa aaggaagaga 480
ctttgtccac agtgtgcagg agactcactc ccagctgctg ggctcctggg acccgtggga 540
agaaccggaa gacgcagccc ctgtggcccc ctccggagcc agggatgtgg aggcgcagct 600
gcggcggctg caggaggaga ggacgtgcaa ggtgtgcctg gaccgcgccg tgtccatcgt 660
ctttgtgccg tgcggccacc tggtctgtgc tgagtgtgcc cccggcctgc agctgtgccc 720
catctgcaga gcccccgtcc gcagccgcgt gcgcaccttc ctgtcctag 769

<210> 23
<211> 756
<212> DNA
<213> Homo sapiens

<400> 23
atgttggggg cccgcctcag gctctgggtc tgtgccttgt gcagcgtctg cagcatgagc 60
gtcctcagag cctatcccaa tgcctcccca ctgctcggct ccagctgggg tggcctgatc 120
cacctgtaca cagccacagc caggaacagc taccacctgc agatccacaa gaatggccat 180
gtggatggcg caccccatca gaccatctac agtgccctga tgatcagatc agaggatgct 240
ggctttgtgg tgattacagg tgtgatgagc agaagatacc tctgcatgga tttcagaggc 300
aacatttttg gatcacacta tttcgacccg gagaactgca ggttccaaca ccagacgctg 360
gaaaacgggt acgacgtcta ccactctcct cagtatcact tcctggtcag tctgggccgg 420
gcgaagagag ccttcctgcc aggcatgaac ccacccccgt actcccagtt cctgtcccgg 480
aggaacgaga tccccctaat tcacttcaac acccccatac cacggcggca cacccggagc 540
gccgaggacg actcggagcg ggacccccctg aacgtgctga agccccgggc ccggatgacc 600
ccggccccgg cctcctgttc acaggagctc ccgagcgccg aggacaacag cccgatggcc 660
agtgacccat taggggtggt caggggcggt cgagtgaaca cgcacgctgg gggaacgggc 720

ccggaaggct gccgcccctt cgccaagttc atctag 756

<210> 24
<211> 592
<212> PRT
<213> Homo sapiens

<400> 24

Met Thr Cys Trp Leu Cys Val Leu Ser Leu Pro Leu Leu Leu Leu Pro
1 5 10 15
Ala Ala Pro Pro Pro Ala Gly Gly Cys Pro Ala Arg Cys Glu Cys Thr
20 25 30
Val Gln Thr Arg Ala Val Ala Cys Thr Arg Arg Arg Leu Thr Ala Val
35 40 45
Pro Asp Gly Ile Pro Ala Glu Thr Arg Leu Leu Glu Leu Ser Arg Asn
50 55 60
Arg Ile Arg Cys Leu Asn Pro Gly Asp Leu Ala Ala Leu Pro Ala Leu
65 70 75 80
Glu Glu Leu Asp Leu Ser Glu Asn Ala Ile Ala His Val Glu Pro Gly
85 90 95
Ala Phe Ala Asn Leu Pro Arg Leu Arg Val Leu Arg Leu Arg Gly Asn
100 105 110
Gln Leu Lys Leu Ile Pro Pro Gly Val Phe Thr Arg Leu Asp Asn Leu
115 120 125
Thr Leu Leu Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr
130 135 140
Thr Phe Gln Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn
145 150 155 160
Asp Leu Val Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu
165 170 175
Glu Glu Leu Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu
180 185 190
Ser Leu Gly His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu
195 200 205
Ala Ile Ala Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu
210 215 220
Leu His Leu Glu Ile Asp Asn Trp Pro Leu Leu Glu Glu Val Ala Ala
225 230 235 240
Gly Ser Leu Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr
245 250 255
Asn Ile Thr Ala Val Pro Ala Ala Ala Leu Arg His Gln Ala His Leu
260 265 270

```
Thr Cys Leu Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly
        275                 280                 285
Ser Phe Arg Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala
    290                 295                 300
Leu Leu Ala Val Val Glu Pro Gln Ala Phe Leu Gly Leu Arg Gln Ile
305                 310                 315                 320
Arg Leu Leu Asn Leu Ser Asn Asn Leu Leu Ser Thr Leu Glu Glu Ser
                325                 330                 335
Thr Phe His Ser Val Asn Thr Leu Glu Thr Leu Arg Val Asp Gly Asn
            340                 345                 350
Pro Leu Ala Cys Asp Cys Arg Leu Leu Trp Ile Val Gln Arg Arg Lys
        355                 360                 365
Thr Leu Asn Phe Asp Gly Arg Leu Pro Ala Cys Ala Thr Pro Ala Glu
    370                 375                 380
Val Arg Gly Asp Ala Leu Arg Asn Leu Pro Asp Ser Val Leu Phe Glu
385                 390                 395                 400
Tyr Phe Val Cys Arg Lys Pro Lys Ile Arg Glu Arg Arg Leu Gln Arg
                405                 410                 415
Val Thr Ala Thr Ala Gly Glu Asp Val Arg Phe Leu Cys Arg Ala Glu
            420                 425                 430
Gly Glu Pro Ala Pro Thr Val Ala Trp Val Thr Pro Gln His Arg Pro
        435                 440                 445
Val Thr Ala Thr Ser Ala Gly Arg Ala Arg Val Leu Pro Gly Gly Thr
    450                 455                 460
Leu Glu Ile Gln Asp Ala Arg Pro Gln Asp Ser Gly Thr Tyr Thr Cys
465                 470                 475                 480
Val Ala Ser Asn Ala Gly Gly Asn Asp Thr Tyr Phe Ala Thr Leu Thr
                485                 490                 495
Val Arg Pro Glu Pro Ala Ala Asn Arg Thr Pro Gly Glu Ala His Asn
            500                 505                 510
Glu Thr Leu Ala Ala Leu Arg Ala Pro Leu Asp Leu Thr Thr Ile Leu
        515                 520                 525
Val Ser Thr Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu Phe
    530                 535                 540
Cys Phe Val Leu Leu Phe Val Trp Ser Arg Gly Arg Gly Gln His Lys
545                 550                 555                 560
Asn Asn Phe Ser Val Glu Tyr Ser Phe Arg Lys Val Asp Gly Pro Ala
                565                 570                 575
Ala Ala Ala Gly Gln Gly Gly Ala Arg Lys Phe Asn Met Lys Met Ile
            580                 585                 590
```

<210> 25

<211> 653
<212> PRT
<213> Homo sapiens

<400> 25

```
Met Lys Leu Leu Trp Gln Val Thr Val His His His Thr Trp Asn Ala
 1               5                  10                  15
Ile Leu Leu Pro Phe Val Tyr Leu Thr Ala Gln Val Trp Ile Leu Cys
            20                  25                  30
Ala Ala Ile Ala Ala Ala Ala Ser Ala Gly Pro Gln Asn Cys Pro Ser
        35                  40                  45
Val Cys Ser Cys Ser Asn Gln Phe Ser Lys Val Val Cys Thr Arg Arg
    50                  55                  60
Gly Leu Ser Glu Val Pro Gln Gly Ile Pro Ser Asn Thr Arg Tyr Leu
65                  70                  75                  80
Asn Leu Met Glu Asn Asn Ile Gln Met Ile Gln Ala Asp Thr Phe Arg
                85                  90                  95
His Leu His His Leu Glu Val Leu Gln Leu Gly Arg Asn Ser Ile Arg
            100                 105                 110
Gln Ile Glu Val Gly Ala Phe Asn Gly Leu Ala Ser Leu Asn Thr Leu
        115                 120                 125
Glu Leu Phe Asp Asn Trp Leu Thr Val Ile Pro Ser Gly Ala Phe Glu
    130                 135                 140
Tyr Leu Ser Lys Leu Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu
145                 150                 155                 160
Ser Ile Pro Ser Tyr Ala Phe Asn Arg Val Pro Ser Leu Met Arg Leu
            165                 170                 175
Asp Leu Gly Glu Leu Lys Lys Leu Glu Tyr Ile Ser Glu Gly Ala Phe
            180                 185                 190
Glu Gly Leu Phe Asn Leu Lys Tyr Leu Asn Leu Gly Met Cys Asn Ile
        195                 200                 205
Lys Asp Met Pro Asn Leu Thr Pro Leu Val Gly Leu Glu Glu Leu Glu
    210                 215                 220
Met Ser Gly Asn His Phe Pro Glu Ile Arg Pro Gly Ser Phe His Gly
225                 230                 235                 240
Leu Ser Ser Leu Lys Lys Leu Trp Val Met Asn Ser Gln Val Ser Leu
                245                 250                 255
Ile Glu Arg Asn Ala Phe Asp Gly Leu Ala Ser Leu Val Glu Leu Asn
            260                 265                 270
Leu Ala His Asn Asn Leu Ser Ser Leu Pro His Asp Leu Phe Thr Pro
        275                 280                 285
Leu Arg Tyr Leu Val Glu Leu His Leu His His Asn Pro Trp Asn Cys
```

```
    290                 295                 300
Asp Cys Asp Ile Leu Trp Leu Ala Trp Trp Leu Arg Glu Tyr Ile Pro
305                 310                 315                 320
Thr Asn Ser Thr Cys Cys Gly Arg Cys His Ala Pro Met His Met Arg
                325                 330                 335
Gly Arg Tyr Leu Val Glu Val Asp Gln Ala Ser Phe Gln Cys Ser Ala
            340                 345                 350
Pro Phe Ile Met Asp Ala Pro Arg Asp Leu Asn Ile Ser Glu Gly Arg
        355                 360                 365
Met Ala Glu Leu Lys Cys Arg Thr Pro Pro Met Ser Ser Val Lys Trp
    370                 375                 380
Leu Leu Pro Asn Gly Thr Val Leu Ser His Ala Ser Arg His Pro Arg
385                 390                 395                 400
Ile Ser Val Leu Asn Asp Gly Thr Leu Asn Phe Ser His Val Leu Leu
                405                 410                 415
Ser Asp Thr Gly Val Tyr Thr Cys Met Val Thr Asn Val Ala Gly Asn
            420                 425                 430
Ser Asn Ala Ser Ala Tyr Leu Asn Val Ser Thr Ala Glu Leu Asn Thr
        435                 440                 445
Ser Asn Tyr Ser Phe Phe Thr Thr Val Thr Val Glu Thr Thr Glu Ile
    450                 455                 460
Ser Pro Glu Asp Thr Thr Arg Lys Tyr Lys Pro Val Pro Thr Thr Ser
465                 470                 475                 480
Thr Gly Tyr Gln Pro Ala Tyr Thr Thr Ser Thr Thr Val Leu Ile Gln
                485                 490                 495
Thr Thr Arg Val Pro Lys Gln Val Ala Val Pro Ala Thr Asp Thr Thr
            500                 505                 510
Asp Lys Met Gln Thr Ser Leu Asp Glu Val Met Lys Thr Thr Lys Ile
        515                 520                 525
Ile Ile Gly Cys Phe Val Ala Val Thr Leu Leu Ala Ala Ala Met Leu
    530                 535                 540
Ile Val Phe Tyr Lys Leu Arg Lys Arg His Gln Gln Arg Ser Thr Val
545                 550                 555                 560
Thr Ala Ala Arg Thr Val Glu Ile Ile Gln Val Asp Glu Asp Ile Pro
                565                 570                 575
Ala Ala Thr Ser Ala Ala Ala Thr Ala Ala Pro Ser Gly Val Ser Gly
            580                 585                 590
Glu Gly Ala Val Val Leu Pro Thr Ile His Asp His Ile Asn Tyr Asn
        595                 600                 605
Thr Tyr Lys Pro Ala His Gly Ala His Trp Thr Glu Asn Ser Leu Gly
    610                 615                 620
Asn Ser Leu His Pro Thr Val Thr Thr Ile Ser Glu Pro Tyr Ile Ile
```

625 630 635 640
Gln Thr His Thr Lys Asp Lys Val Gln Glu Thr Gln Ile
645 650

<210> 26
<211> 70
<212> PRT
<213> Homo sapiens

<400> 26
Met Val Ser Val Cys Arg Pro Trp Pro Ala Val Ala Ile Ala Leu Leu
1 5 10 15
Ala Leu Leu Val Cys Leu Gly Ala Leu Val Asp Thr Cys Pro Ile Lys
20 25 30
Pro Glu Ala Pro Gly Glu Asp Glu Ser Leu Glu Glu Leu Ser His Tyr
35 40 45
Tyr Ala Ser Leu Cys His Tyr Leu Asn Val Val Thr Arg Gln Trp Trp
50 55 60
Glu Gly Ala Asp Met Trp
65 70

<210> 27
<211> 130
<212> PRT
<213> Homo sapiens

<400> 27
Met Lys Leu Ala Phe Leu Phe Leu Gly Pro Met Ala Leu Leu Leu Leu
1 5 10 15
Ala Gly Tyr Gly Cys Val Leu Gly Ala Ser Ser Gly Asn Leu Arg Thr
20 25 30
Phe Val Gly Cys Ala Val Arg Glu Phe Thr Phe Leu Ala Lys Lys Pro
35 40 45
Gly Cys Arg Gly Leu Arg Ile Thr Thr Asp Ala Cys Trp Gly Arg Cys
50 55 60
Glu Thr Trp Glu Lys Pro Ile Leu Glu Pro Pro Tyr Ile Glu Ala His
65 70 75 80
His Arg Val Cys Thr Tyr Asn Glu Thr Lys Gln Val Thr Val Lys Leu
85 90 95
Pro Asn Cys Ala Pro Gly Val Asp Pro Phe Tyr Thr Tyr Pro Val Ala
100 105 110
Ile Arg Cys Asp Cys Gly Ala Cys Ser Thr Ala Thr Thr Glu Cys Glu

115 120 125

Thr Ile
130

<210> 28
<211> 676
<212> PRT
<213> Homo sapiens

<400> 28

Ile Pro Asn Ala Phe Lys Pro Gly Asp Leu Val Phe Pro Lys Ile Lys
1 5 10 15
Gly Tyr Pro Gln Trp Pro Ser Arg Ile Asp Asp Ile Ala Asp Gly Ala
20 25 30
Val Lys Pro Pro Pro Asn Lys Tyr Pro Ile Phe Phe Phe Gly Thr His
35 40 45
Glu Thr Ala Phe Leu Gly Pro Lys Asp Leu Phe Pro Tyr Asp Lys Cys
50 55 60
Lys Asp Lys Tyr Gly Lys Pro Asn Lys Arg Lys Gly Phe Asn Glu Gly
65 70 75 80
Leu Trp Glu Ile Gln Asn Asn Pro His Ala Ser Tyr Ser Ala Pro Pro
85 90 95
Pro Val Ser Ser Ser Asp Ser Glu Ala Pro Glu Ala Asn Pro Ala Asp
100 105 110
Gly Ser Asp Ala Asp Glu Asp Asp Glu Asp Arg Gly Val Met Ala Val
115 120 125
Thr Ala Val Thr Ala Thr Ala Ala Ser Asp Arg Met Glu Ser Asp Ser
130 135 140
Asp Ser Asp Lys Ser Ser Asp Asn Ser Gly Leu Lys Arg Lys Thr Pro
145 150 155 160
Ala Leu Lys Met Ser Val Ser Lys Arg Ala Arg Lys Ala Ser Ser Asp
165 170 175
Leu Asp Gln Ala Ser Val Ser Pro Ser Glu Glu Glu Asn Ser Glu Ser
180 185 190
Ser Ser Glu Ser Glu Lys Thr Ser Asp Gln Asp Phe Thr Pro Glu Lys
195 200 205
Lys Ala Ala Val Arg Ala Pro Arg Arg Gly Pro Leu Gly Gly Arg Lys
210 215 220
Lys Lys Lys Ala Pro Ser Ala Ser Asp Ser Asp Ser Lys Ala Asp Ser
225 230 235 240
Asp Gly Ala Lys Pro Glu Pro Val Ala Met Ala Arg Ser Ala Ser Ser
245 250 255

Ser Ser Ser Ser Ser Ser Ser Ser Asp Ser Asp Val Ser Val Lys Lys
260 265 270
Pro Pro Arg Gly Arg Lys Pro Ala Glu Lys Pro Leu Pro Lys Pro Arg
275 280 285
Gly Arg Lys Pro Lys Pro Glu Arg Pro Pro Ser Ser Ser Ser Ser Asp
290 295 300
Ser Asp Ser Asp Glu Val Asp Arg Ile Ser Glu Trp Lys Arg Arg Asp
305 310 315 320
Glu Ala Arg Arg Arg Glu Leu Glu Ala Arg Arg Arg Arg Glu Gln Glu
325 330 335
Glu Glu Leu Arg Arg Leu Arg Glu Gln Glu Lys Glu Glu Lys Glu Arg
340 345 350
Arg Arg Glu Arg Ala Asp Arg Gly Glu Ala Glu Arg Gly Ser Gly Gly
355 360 365
Ser Ser Gly Asp Glu Leu Arg Glu Asp Asp Glu Pro Val Lys Lys Arg
370 375 380
Gly Arg Lys Gly Arg Gly Arg Gly Pro Pro Ser Ser Ser Asp Ser Glu
385 390 395 400
Pro Glu Ala Glu Leu Glu Arg Glu Ala Lys Lys Ser Ala Lys Lys Pro
405 410 415
Gln Ser Ser Ser Thr Glu Pro Ala Arg Lys Pro Gly Gln Lys Glu Lys
420 425 430
Arg Val Arg Pro Glu Glu Lys Gln Gln Ala Lys Pro Val Lys Val Glu
435 440 445
Arg Thr Arg Lys Arg Ser Glu Gly Phe Ser Met Asp Arg Lys Val Glu
450 455 460
Lys Lys Lys Glu Pro Ser Val Glu Glu Lys Leu Gln Lys Leu His Ser
465 470 475 480
Glu Ile Lys Phe Ala Leu Lys Val Asp Ser Pro Asp Val Lys Arg Cys
485 490 495
Leu Asn Ala Leu Glu Glu Leu Gly Thr Leu Gln Val Thr Ser Gln Ile
500 505 510
Leu Gln Lys Asn Thr Asp Val Val Ala Thr Leu Lys Lys Ile Arg Arg
515 520 525
Tyr Lys Ala Asn Lys Asp Val Met Glu Lys Ala Ala Glu Val Tyr Thr
530 535 540
Arg Leu Lys Ser Arg Val Leu Gly Pro Lys Ile Glu Ala Val Gln Lys
545 550 555 560
Val Asn Lys Ala Gly Met Glu Lys Glu Lys Ala Glu Glu Lys Leu Ala
565 570 575
Gly Glu Glu Leu Ala Gly Glu Glu Leu Ala Gly Glu Glu Ala Pro Gln
580 585 590

```
Glu Lys Ala Glu Asp Lys Pro Ser Thr Asp Leu Ser Ala Pro Val Asn
        595                 600                 605
Gly Glu Ala Thr Ser Gln Lys Gly Glu Ser Ala Glu Asp Lys Glu His
    610                 615                 620
Glu Glu Gly Arg Asp Ser Glu Glu Gly Pro Arg Cys Gly Ser Ser Glu
625                 630                 635                 640
Asp Leu His Asp Ser Val Arg Glu Gly Pro Asp Leu Asp Arg Pro Gly
                645                 650                 655
Ser Asp Arg Gln Glu Arg Glu Arg Ala Arg Gly Asp Ser Glu Ala Leu
            660                 665                 670
Asp Glu Glu Ser
        675
```

<210> 29
<211> 717
<212> PRT
<213> Homo sapiens

<400> 29

```
Met Ala Val Leu Asp Leu Arg Glu Leu Arg Arg Gly Asp Leu Gly Gly
 1               5                  10                  15
Val Gln Gly Leu Lys Glu Leu Arg Arg Gln Trp Ser Gly Gly Pro Gly
            20                  25                  30
Pro Glu Glu Ala Ala Leu Trp Gly Ser Gly Ala Ser Val Pro Glu Gly
        35                  40                  45
Ala Ala Pro Trp Gly Ser Gly Val Ala Leu Ala Gln Arg Glu Pro Arg
    50                  55                  60
Leu Ile Asp Asp Ile Ala Asp Gly Ala Val Lys Pro Pro Pro Asn Lys
65                  70                  75                  80
Tyr Pro Ile Phe Phe Phe Gly Thr His Glu Thr Ala Phe Leu Gly Pro
                85                  90                  95
Lys Asp Leu Phe Pro Tyr Asp Lys Cys Lys Asp Lys Tyr Gly Lys Pro
            100                 105                 110
Asn Lys Arg Lys Gly Phe Asn Glu Gly Leu Trp Glu Ile Gln Asn Asn
        115                 120                 125
Pro His Ala Ser Tyr Ser Ala Pro Pro Pro Val Ser Ser Ser Asp Ser
    130                 135                 140
Glu Ala Pro Glu Ala Asn Pro Ala Asp Gly Ser Asp Ala Asp Glu Asp
145                 150                 155                 160
Asp Glu Asp Arg Gly Val Met Ala Val Thr Ala Val Thr Ala Thr Ala
                165                 170                 175
Ala Ser Asp Arg Met Glu Ser Asp Ser Asp Ser Asp Lys Ser Ser Asp
```

```
            180                 185                 190
Asn Ser Gly Leu Lys Arg Lys Thr Pro Ala Leu Lys Met Ser Val Ser
        195                 200                 205
Lys Arg Ala Arg Lys Ala Ser Ser Asp Leu Asp Gln Ala Ser Val Ser
    210                 215                 220
Pro Ser Glu Glu Glu Asn Ser Glu Ser Ser Ser Glu Ser Glu Lys Thr
225                 230                 235                 240
Ser Asp Gln Asp Phe Thr Pro Glu Lys Lys Ala Ala Val Arg Ala Pro
                245                 250                 255
Arg Arg Gly Pro Leu Gly Gly Arg Lys Lys Lys Lys Ala Pro Ser Ala
            260                 265                 270
Ser Asp Ser Asp Ser Lys Ala Asp Ser Asp Gly Ala Lys Pro Glu Pro
        275                 280                 285
Val Ala Met Ala Arg Ser Ala Ser Ser Ser Ser Ser Ser Ser Ser Ser
    290                 295                 300
Ser Asp Ser Asp Val Ser Val Lys Lys Pro Pro Arg Gly Arg Lys Pro
305                 310                 315                 320
Ala Glu Lys Pro Leu Pro Lys Pro Arg Gly Arg Lys Pro Lys Pro Glu
                325                 330                 335
Arg Pro Pro Ser Ser Ser Ser Ser Asp Ser Asp Ser Asp Glu Val Asp
            340                 345                 350
Arg Ile Ser Glu Trp Lys Arg Arg Asp Glu Ala Arg Arg Arg Glu Leu
        355                 360                 365
Glu Ala Arg Arg Arg Arg Glu Gln Glu Glu Glu Leu Arg Arg Leu Arg
    370                 375                 380
Glu Gln Glu Lys Glu Glu Lys Glu Arg Arg Arg Glu Arg Ala Asp Arg
385                 390                 395                 400
Gly Glu Ala Glu Arg Gly Ser Gly Gly Ser Ser Gly Asp Glu Leu Arg
                405                 410                 415
Glu Asp Asp Glu Pro Val Lys Lys Arg Gly Arg Lys Gly Arg Gly Arg
            420                 425                 430
Gly Pro Pro Ser Ser Ser Asp Ser Glu Pro Glu Ala Glu Leu Glu Arg
        435                 440                 445
Glu Ala Lys Lys Ser Ala Lys Lys Pro Gln Ser Ser Ser Thr Glu Pro
    450                 455                 460
Ala Arg Lys Pro Gly Gln Lys Glu Lys Arg Val Arg Pro Glu Glu Lys
465                 470                 475                 480
Gln Gln Ala Lys Pro Val Lys Val Glu Arg Thr Arg Lys Arg Ser Glu
                485                 490                 495
Gly Phe Ser Met Asp Arg Lys Val Glu Lys Lys Lys Glu Pro Ser Val
            500                 505                 510
Glu Glu Lys Leu Gln Lys Leu His Ser Glu Ile Lys Phe Ala Leu Lys
```

```
        515                 520                 525
Val Asp Ser Pro Asp Val Lys Arg Cys Leu Asn Ala Leu Glu Glu Leu
    530                 535                 540
Gly Thr Leu Gln Val Thr Ser Gln Ile Leu Gln Lys Asn Thr Asp Val
545                 550                 555                 560
Val Ala Thr Leu Lys Lys Ile Arg Arg Tyr Lys Ala Asn Lys Asp Val
                565                 570                 575
Met Glu Lys Ala Ala Glu Val Tyr Thr Arg Leu Lys Ser Arg Val Leu
            580                 585                 590
Gly Pro Lys Ile Glu Ala Val Gln Lys Val Asn Lys Ala Gly Met Glu
        595                 600                 605
Lys Glu Lys Ala Glu Glu Lys Leu Ala Gly Glu Glu Leu Ala Gly Glu
    610                 615                 620
Glu Leu Ala Gly Glu Glu Ala Pro Gln Glu Lys Ala Glu Asp Lys Pro
625                 630                 635                 640
Ser Thr Asp Leu Ser Ala Pro Val Asn Gly Glu Ala Thr Ser Gln Lys
                645                 650                 655
Gly Glu Ser Ala Glu Asp Lys Glu His Glu Glu Gly Arg Asp Ser Glu
            660                 665                 670
Glu Gly Pro Arg Cys Gly Ser Ser Glu Asp Leu His Asp Ser Val Arg
        675                 680                 685
Glu Gly Pro Asp Leu Asp Arg Pro Gly Ser Asp Arg Gln Glu Arg Glu
    690                 695                 700
Arg Ala Arg Gly Asp Ser Glu Ala Leu Asp Glu Glu Ser
705                 710                 715
```

<210> 30
<211> 288
<212> PRT
<213> Homo sapiens

<400> 30

```
Met Phe Val Leu Leu Tyr Val Thr Ser Phe Ala Ile Cys Ala Ser Gly
 1               5                  10                  15
Gln Pro Arg Gly Asn Gln Leu Lys Gly Glu Asn Tyr Ser Pro Arg Tyr
            20                  25                  30
Ile Cys Ser Ile Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Ala
        35                  40                  45
Asn Gly Ser Pro Gly Pro His Gly Arg Ile Gly Leu Pro Gly Arg Asp
    50                  55                  60
Gly Arg Asp Gly Arg Lys Gly Glu Lys Gly Glu Lys Gly Thr Ala Leu
65                  70                  75                  80
```

```
Arg Gly Lys Thr Gly Pro Leu Gly Leu Ala Gly Glu Lys Gly Asp Gln
                85                  90                  95
Gly Glu Thr Gly Lys Lys Gly Pro Ile Gly Pro Glu Gly Glu Lys Gly
            100                 105                 110
Glu Val Gly Pro Ile Gly Pro Pro Gly Pro Lys Gly Asp Arg Gly Glu
        115                 120                 125
Gln Gly Asp Pro Gly Leu Pro Gly Val Cys Arg Cys Gly Ser Ile Val
    130                 135                 140
Leu Lys Ser Ala Phe Ser Val Gly Ile Thr Thr Ser Tyr Pro Glu Glu
145                 150                 155                 160
Arg Leu Pro Ile Ile Phe Asn Lys Val Leu Phe Asn Glu Gly Glu His
                165                 170                 175
Tyr Asn Pro Ala Thr Gly Lys Phe Ile Cys Ala Phe Pro Gly Ile Tyr
            180                 185                 190
Tyr Phe Ser Tyr Asp Ile Thr Leu Ala Asn Lys His Leu Ala Ile Gly
        195                 200                 205
Leu Val His Asn Gly Gln Tyr Arg Ile Lys Thr Phe Asp Ala Asn Thr
    210                 215                 220
Gly Asn His Asp Val Ala Ser Gly Ser Thr Val Ile Tyr Leu Gln Pro
225                 230                 235                 240
Glu Asp Glu Val Trp Leu Glu Ile Phe Phe Thr Asp Gln Asn Gly Leu
                245                 250                 255
Phe Ser Asp Pro Gly Trp Ala Asp Ser Leu Phe Ser Gly Phe Leu Leu
            260                 265                 270
Tyr Val Asp Thr Asp Tyr Leu Asp Ser Ile Ser Glu Asp Asp Glu Leu
        275                 280                 285
```

<210> 31
<211> 303
<212> PRT
<213> Homo sapiens

<400> 31

```
Met Gly Lys Glu Asp Thr Gln Glu Thr Arg Thr Glu Pro Lys Met Phe
 1               5                  10                  15
Val Leu Leu Tyr Val Thr Ser Phe Ala Ile Cys Ala Ser Gly Gln Pro
            20                  25                  30
Arg Gly Asn Gln Leu Lys Gly Glu Asn Tyr Ser Pro Arg Tyr Ile Cys
        35                  40                  45
Ser Ile Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Ala Asn Gly
    50                  55                  60
Ser Pro Gly Pro His Gly Arg Ile Gly Leu Pro Gly Arg Asp Gly Arg
```

65 70 75 80
Asp Gly Arg Lys Gly Glu Lys Gly Glu Lys Gly Thr Ala Gly Leu Arg
85 90 95
Gly Lys Thr Gly Pro Leu Gly Leu Ala Gly Glu Lys Gly Asp Gln Gly
100 105 110
Glu Thr Gly Lys Lys Gly Pro Ile Gly Pro Glu Gly Glu Lys Gly Glu
115 120 125
Val Gly Pro Ile Gly Pro Pro Gly Pro Lys Gly Asp Arg Gly Glu Gln
130 135 140
Gly Asp Pro Gly Leu Pro Gly Val Cys Arg Cys Gly Ser Ile Val Leu
145 150 155 160
Lys Ser Ala Phe Ser Val Gly Ile Thr Thr Ser Tyr Pro Glu Glu Arg
165 170 175
Leu Pro Ile Ile Phe Asn Lys Val Leu Phe Asn Glu Gly Glu His Tyr
180 185 190
Asn Pro Ala Thr Gly Lys Phe Ile Cys Ala Phe Pro Gly Ile Tyr Tyr
195 200 205
Phe Ser Tyr Asp Ile Thr Leu Ala Asn Lys His Leu Ala Ile Gly Leu
210 215 220
Val His Asn Gly Gln Tyr Arg Ile Lys Thr Phe Asp Ala Asn Thr Gly
225 230 235 240
Asn His Asp Val Ala Ser Gly Ser Thr Val Ile Tyr Leu Gln Pro Glu
245 250 255
Asp Glu Val Trp Leu Glu Ile Phe Phe Thr Asp Gln Asn Gly Leu Phe
260 265 270
Ser Asp Pro Gly Trp Ala Asp Ser Leu Phe Ser Gly Phe Leu Leu Tyr
275 280 285
Val Asp Thr Asp Tyr Leu Asp Ser Ile Ser Glu Asp Asp Glu Leu
290 295 300

<210> 32
<211> 88
<212> PRT
<213> Homo sapiens

<400> 32
Met Ser Leu Gln Ala Asp Phe Asp Met Val Thr Glu Asp Val Arg Lys
1 5 10 15
Leu Lys Thr Arg Pro Asp Asp Glu Glu Leu Lys Glu Leu Tyr Gly Leu
20 25 30
Tyr Lys Gln Ala Val Ile Gly Asn Ile Asn Ile Glu Cys Ser Glu Met
35 40 45

Leu Glu Leu Lys Gly Lys Ala Lys Trp Glu Ala Gln Asn Pro Gln Lys
50 55 60
Gly Leu Ser Glu Glu Asp Met Met Arg Ala Phe Ile Ser Lys Ala Glu
65 70 75 80
Glu Leu Ile Glu Lys Tyr Gly Ile
85

<210> 33
<211> 422
<212> PRT
<213> Homo sapiens

<400> 33
Met His Gly Gly Ser Trp Gly Ser Val Cys Asp Asp Asp Trp Asp Val
1 5 10 15
Val Asp Ala Asn Val Val Cys Arg Gln Leu Gly Cys Gly Leu Ala Leu
20 25 30
Pro Val Pro Arg Pro Leu Ala Phe Gly Gln Gly Arg Gly Pro Ile Leu
35 40 45
Leu Asp Asn Val Glu Cys Arg Gly Gln Glu Ala Ala Leu Ser Glu Cys
50 55 60
Gly Ser Arg Gly Trp Gly Val His Asn Cys Phe His Tyr Glu Asp Val
65 70 75 80
Ala Val Leu Cys Asp Gly Glu Gly Ser Val Arg Leu Val Gly Gly Ala
85 90 95
Asn Leu Cys Gln Gly Arg Val Glu Ile Leu His Ser Gly Leu Trp Gly
100 105 110
Thr Val Cys Asp Asp Asp Trp Gly Leu Pro Asp Ala Ala Val Val Cys
115 120 125
Arg Gln Leu Gly Cys Gly Ala Ala Met Ala Ala Thr Thr Asn Ala Phe
130 135 140
Phe Gly Tyr Gly Thr Gly His Ile Leu Leu Asp Asn Val His Cys Glu
145 150 155 160
Gly Gly Glu Pro Arg Leu Ala Ala Cys Gln Ser Leu Gly Trp Gly Val
165 170 175
His Asn Cys Gly His His Glu Asp Ala Gly Ala Leu Cys Ala Gly Ala
180 185 190
Gly Ser Arg Gly Asp Gly Arg Gly Arg Gly Ser Pro Ser Gly Arg Gly
195 200 205
Pro Val Arg Pro Ala Gly Gly Arg Leu Arg Leu Val Gly Gly Pro Gly
210 215 220
Pro Cys Arg Gly Arg Val Glu Val Leu His Ala Gly Gly Trp Gly Thr

225 230 235 240
Val Cys Asp Asp Asp Trp Asp Phe Ala Asp Ala Arg Val Ala Cys Arg
245 250 255
Glu Ala Gly Cys Gly Pro Ala Leu Gly Ala Thr Gly Leu Gly His Phe
260 265 270
Gly Tyr Gly Arg Gly Pro Val Leu Leu Asp Asn Val Gly Cys Ala Gly
275 280 285
Thr Glu Ala Arg Leu Ser Asp Cys Phe His Leu Gly Trp Gly Gln His
290 295 300
Asn Cys Gly His His Glu Asp Ala Gly Ala Leu Cys Ala Gly His Leu
305 310 315 320
Arg Leu Val Asn Gly Ala His Arg Cys Glu Gly Arg Val Glu Leu Tyr
325 330 335
Leu Gly Gln Arg Trp Gly Thr Val Cys Asp Asp Ala Trp Asp Leu Arg
340 345 350
Ala Ala Gly Val Leu Cys Arg Gln Leu Gly Cys Gly Gln Ala Leu Ala
355 360 365
Ala Pro Gly Glu Ala His Phe Gly Pro Gly Arg Gly Pro Ile Leu Leu
370 375 380
Asp Asn Val Lys Cys Arg Gly Glu Glu Ser Ala Leu Leu Leu Cys Ser
385 390 395 400
His Ile Arg Trp Asp Ala His Asn Cys Asp His Ser Glu Asp Ala Ser
405 410 415
Val Leu Cys Gln Pro Ser
420

<210> 34
<211> 552
<212> PRT
<213> Homo sapiens

<400> 34
Met Ala Thr Leu Pro Glu Lys Ala Leu Lys Glu Ala Trp Lys Gly Leu
1 5 10 15
Ile Pro Arg Phe Pro Trp Leu His Gly Lys Ala Glu Leu Arg Leu Val
20 25 30
Gly Gly Pro Ser Arg Cys Arg Gly Arg Leu Glu Val Met His Gly Gly
35 40 45
Ser Trp Gly Ser Val Cys Asp Asp Asp Trp Asp Val Val Asp Ala Asn
50 55 60
Val Val Cys Arg Gln Leu Gly Cys Gly Leu Ala Leu Pro Val Pro Arg
65 70 75 80

```
Pro Leu Ala Phe Gly Gln Gly Arg Gly Pro Ile Leu Leu Asp Asn Val
                85                  90                  95
Glu Cys Arg Gly Gln Glu Ala Ala Leu Ser Glu Cys Gly Ser Arg Gly
            100                 105                 110
Trp Gly Val His Asn Cys Phe His Tyr Glu Asp Val Ala Val Leu Cys
        115                 120                 125
Asp Glu Phe Leu Pro Thr Gln Pro Pro Thr Arg Lys Met Leu Thr Ser
    130                 135                 140
Arg Ala Pro Pro Thr Thr Leu Pro Asn Gly Lys Ser Glu Gly Ser Val
145                 150                 155                 160
Arg Leu Val Gly Gly Ala Asn Leu Cys Gln Gly Arg Val Glu Ile Leu
                165                 170                 175
His Ser Gly Leu Trp Gly Thr Val Cys Asp Asp Asp Trp Gly Leu Pro
            180                 185                 190
Asp Ala Ala Val Val Cys Arg Gln Leu Gly Cys Gly Ala Ala Met Ala
        195                 200                 205
Ala Thr Thr Asn Ala Phe Phe Gly Tyr Gly Thr Gly His Ile Leu Leu
    210                 215                 220
Asp Asn Val His Cys Glu Gly Gly Glu Pro Arg Leu Ala Ala Cys Gln
225                 230                 235                 240
Ser Leu Gly Trp Gly Val His Asn Cys Gly His His Glu Asp Ala Gly
                245                 250                 255
Ala Leu Cys Ala Gly Leu Gly Pro Pro Thr Leu Thr Ala Leu Pro Ser
            260                 265                 270
Ser Ala Thr Arg Glu Asp Trp Ala Trp Gln Thr Asp Pro Ser Ala Thr
        275                 280                 285
Gly Val Gly Pro Gln Pro Ser Arg Glu Thr Ala Leu Leu Thr Thr Ala
    290                 295                 300
Ala Trp Ala Ala Gly Lys Lys Ser Gly Arg Leu Arg Leu Val Gly Gly
305                 310                 315                 320
Pro Gly Pro Cys Arg Gly Arg Val Glu Val Leu His Ala Gly Gly Trp
                325                 330                 335
Gly Thr Val Cys Asp Asp Asp Trp Asp Phe Ala Asp Ala Arg Val Ala
            340                 345                 350
Cys Arg Glu Ala Gly Cys Gly Pro Ala Leu Gly Ala Thr Gly Leu Gly
        355                 360                 365
His Phe Gly Tyr Gly Arg Gly Pro Val Leu Leu Asp Asn Val Gly Cys
    370                 375                 380
Ala Gly Thr Glu Ala Arg Leu Ser Asp Cys Phe His Leu Gly Trp Gly
385                 390                 395                 400
Gln His Asn Cys Gly His His Glu Asp Ala Gly Ala Leu Cys Ala Gly
                405                 410                 415
```

```
Glu Ala Asp Ser Glu Gly Pro Glu Glu Leu Gly Leu Gln Val Gln Gln
            420                 425                 430
Asp Gly Ser Glu Thr Thr Arg Val Pro Thr Pro Arg Pro Arg Asp Gly
        435                 440                 445
His Leu Arg Leu Val Asn Gly Ala His Arg Cys Glu Gly Arg Val Glu
    450                 455                 460
Leu Tyr Leu Gly Gln Arg Trp Gly Thr Val Cys Asp Asp Ala Trp Asp
465                 470                 475                 480
Leu Arg Ala Ala Gly Val Leu Cys Arg Gln Leu Gly Cys Gly Gln Ala
                485                 490                 495
Leu Ala Ala Pro Gly Glu Ala His Phe Gly Pro Gly Arg Gly Pro Ile
            500                 505                 510
Leu Leu Asp Asn Val Lys Cys Arg Gly Glu Glu Ser Ala Leu Leu Leu
        515                 520                 525
Cys Ser His Ile Arg Trp Asp Ala His Asn Cys Asp His Ser Glu Asp
    530                 535                 540
Ala Ser Val Leu Cys Gln Pro Ser
545                 550
```

<210> 35
<211> 1709
<212> PRT
<213> Homo sapiens

<400> 35

```
Met Gly Phe Leu Pro Lys Leu Leu Leu Leu Ala Ser Phe Phe Pro Ala
 1               5                  10                  15
Gly Gln Ala Ser Trp Gly Val Ser Ser Pro Gln Asp Val Gln Gly Val
            20                  25                  30
Lys Gly Ser Cys Leu Leu Ile Pro Cys Ile Phe Ser Phe Pro Ala Asp
        35                  40                  45
Val Glu Val Pro Asp Gly Ile Thr Ala Ile Trp Tyr Tyr Asp Tyr Ser
    50                  55                  60
Gly Gln Arg Gln Val Val Ser His Ser Ala Asp Pro Lys Leu Val Glu
65                  70                  75                  80
Ala Arg Phe Arg Gly Arg Thr Glu Phe Met Gly Asn Pro Glu His Arg
                85                  90                  95
Val Cys Asn Leu Leu Leu Lys Asp Leu Gln Pro Glu Asp Ser Gly Ser
            100                 105                 110
Tyr Asn Phe Arg Phe Glu Ile Ser Glu Val Asn Arg Trp Ser Asp Val
        115                 120                 125
Lys Gly Thr Leu Val Thr Val Thr Glu Glu Pro Arg Val Pro Thr Ile
```

```
    130                 135                 140
Ala Ser Pro Val Glu Leu Leu Glu Gly Thr Glu Val Asp Phe Asn Cys
145                 150                 155                 160
Ser Thr Pro Tyr Val Cys Leu Gln Glu Gln Val Arg Leu Gln Trp Gln
                165                 170                 175
Gly Gln Asp Pro Ala Arg Ser Val Thr Phe Asn Ser Gln Lys Phe Glu
            180                 185                 190
Pro Thr Gly Val Gly His Leu Glu Thr Leu His Met Ala Met Ser Trp
        195                 200                 205
Gln Asp His Gly Arg Ile Leu Arg Cys Gln Leu Ser Val Ala Asn His
    210                 215                 220
Arg Ala Gln Ser Glu Ile His Leu Gln Val Lys Tyr Ala Pro Lys Gly
225                 230                 235                 240
Val Lys Ile Leu Leu Ser Pro Ser Gly Arg Asn Ile Leu Pro Gly Glu
                245                 250                 255
Leu Val Thr Leu Thr Cys Gln Val Asn Ser Ser Tyr Pro Ala Val Ser
            260                 265                 270
Ser Ile Lys Trp Leu Lys Asp Gly Val Arg Leu Gln Thr Lys Thr Gly
        275                 280                 285
Val Leu His Leu Pro Gln Ala Ala Trp Ser Asp Ala Gly Val Tyr Thr
    290                 295                 300
Cys Gln Ala Glu Asn Gly Val Gly Ser Leu Val Ser Pro Pro Ile Ser
305                 310                 315                 320
Leu His Ile Phe Met Ala Glu Val Gln Val Ser Pro Ala Gly Pro Ile
                325                 330                 335
Leu Glu Asn Gln Thr Val Thr Leu Val Cys Asn Thr Pro Asn Glu Ala
            340                 345                 350
Pro Ser Asp Leu Arg Tyr Ser Trp Tyr Lys Asn His Val Leu Leu Glu
        355                 360                 365
Asp Ala His Ser His Thr Leu Arg Leu His Leu Ala Thr Arg Ala Asp
    370                 375                 380
Thr Gly Phe Tyr Phe Cys Glu Val Gln Asn Val His Gly Ser Glu Arg
385                 390                 395                 400
Ser Gly Pro Val Ser Val Val Val Asn Leu Leu Thr Ala Phe Leu Glu
                405                 410                 415
Thr Gln Ala Gly Leu Val Gly Ile Leu His Cys Ser Val Val Ser Glu
            420                 425                 430
Pro Leu Ala Thr Leu Val Leu Ser His Gly Gly His Ile Leu Ala Ser
        435                 440                 445
Thr Ser Gly Asp Ser Asp His Ser Pro Arg Phe Ser Gly Thr Ser Gly
    450                 455                 460
Pro Asn Ser Leu Arg Leu Glu Ile Arg Asp Leu Glu Glu Thr Asp Ser
```

```
465                 470                 475                 480
Gly Glu Tyr Lys Cys Ser Ala Thr Asn Ser Leu Gly Asn Ala Thr Ser
                485                 490                 495
Thr Leu Asp Phe His Ala Asn Ala Ala Arg Leu Leu Ile Ser Pro Ala
            500                 505                 510
Ala Glu Val Val Glu Gly Gln Ala Val Thr Leu Ser Cys Arg Ser Gly
        515                 520                 525
Leu Ser Pro Thr Pro Asp Ala Arg Phe Ser Trp Tyr Leu Asn Gly Ala
    530                 535                 540
Leu Leu His Glu Gly Pro Gly Ser Ser Leu Leu Leu Pro Ala Ala Ser
545                 550                 555                 560
Ser Thr Asp Ala Gly Ser Tyr His Cys Arg Ala Arg Asp Gly His Ser
                565                 570                 575
Ala Ser Gly Pro Ser Ser Pro Ala Val Leu Thr Val Leu Tyr Pro Pro
            580                 585                 590
Arg Gln Pro Thr Phe Thr Thr Arg Leu Asp Leu Asp Ala Ala Gly Ala
        595                 600                 605
Gly Ala Gly Arg Arg Gly Leu Leu Leu Cys Arg Val Asp Ser Asp Pro
    610                 615                 620
Pro Ala Arg Leu Gln Leu Leu His Lys Asp Arg Val Val Ala Thr Ser
625                 630                 635                 640
Leu Pro Ser Gly Gly Gly Cys Ser Thr Cys Gly Gly Cys Ser Pro Arg
                645                 650                 655
Met Lys Val Thr Lys Ala Pro Asn Leu Leu Arg Val Glu Ile His Asn
            660                 665                 670
Pro Leu Leu Glu Glu Glu Gly Leu Tyr Leu Cys Glu Ala Ser Asn Ala
        675                 680                 685
Leu Gly Asn Ala Ser Thr Ser Ala Thr Phe Asn Gly Gln Ala Thr Val
    690                 695                 700
Leu Ala Ile Ala Pro Ser His Thr Leu Gln Glu Gly Thr Glu Ala Asn
705                 710                 715                 720
Leu Thr Cys Asn Val Ser Arg Glu Ala Ala Gly Ser Pro Ala Asn Phe
                725                 730                 735
Ser Trp Phe Arg Asn Gly Val Leu Trp Ala Gln Gly Pro Leu Glu Thr
            740                 745                 750
Val Thr Leu Leu Pro Val Ala Arg Thr Asp Ala Ala Leu Tyr Ala Cys
        755                 760                 765
Arg Ile Leu Thr Glu Ala Gly Ala Gln Leu Ser Thr Pro Val Leu Leu
    770                 775                 780
Ser Val Leu Tyr Pro Pro Asp Arg Pro Lys Leu Ser Ala Leu Leu Asp
785                 790                 795                 800
Met Gly Gln Gly His Met Ala Leu Phe Ile Cys Thr Val Asp Ser Arg
```

Pro Leu Ala Leu Leu Ala Leu Phe His Gly Glu His Leu Leu Ala Thr
820 825 830
Ser Leu Gly Pro Gln Val Pro Ser His Gly Arg Phe Gln Ala Lys Ala
835 840 845
Glu Ala Asn Ser Leu Lys Leu Glu Val Arg Glu Leu Gly Leu Gly Asp
850 855 860
Ser Gly Ser Tyr Arg Cys Glu Ala Thr Asn Val Leu Gly Ser Ser Asn
865 870 875 880
Thr Ser Leu Phe Phe Gln Val Arg Gly Ala Trp Val Gln Val Ser Pro
885 890 895
Ser Pro Glu Leu Gln Glu Gly Gln Ala Val Val Leu Ser Cys Gln Val
900 905 910
His Thr Gly Val Pro Glu Gly Thr Ser Tyr Arg Trp Tyr Arg Asp Gly
915 920 925
Gln Pro Leu Gln Glu Ser Thr Ser Ala Thr Leu Arg Phe Ala Ala Ile
930 935 940
Thr Leu Thr Gln Ala Gly Ala Tyr His Cys Gln Ala Gln Ala Pro Gly
945 950 955 960
Ser Ala Thr Thr Ser Leu Ala Ala Pro Ile Ser Leu His Val Ser Tyr
965 970 975
Ala Pro Arg His Val Thr Leu Thr Thr Leu Met Asp Thr Gly Pro Gly
980 985 990
Arg Leu Gly Leu Leu Leu Cys Arg Val Asp Ser Asp Pro Pro Ala Gln
995 1000 1005
Leu Arg Leu Leu His Gly Asp Arg Leu Val Ala Ser Thr Leu Gln Gly
1010 1015 1020
Val Gly Gly Pro Glu Gly Ser Ser Pro Arg Leu His Val Ala Val Ala
1025 1030 1035 1040
Pro Asn Thr Leu Arg Leu Glu Ile His Gly Ala Met Leu Glu Asp Glu
1045 1050 1055
Gly Val Tyr Ile Cys Glu Ala Ser Asn Thr Leu Gly Gln Ala Ser Ala
1060 1065 1070
Ser Ala Asp Phe Asp Ala Gln Ala Val Asn Val Gln Val Trp Pro Gly
1075 1080 1085
Ala Thr Val Arg Glu Gly Gln Leu Val Asn Leu Thr Cys Leu Val Trp
1090 1095 1100
Thr Thr His Pro Ala Gln Leu Thr Tyr Thr Trp Tyr Gln Asp Gly Gln
1105 1110 1115 1120
Gln Arg Leu Asp Ala His Ser Ile Pro Leu Pro Asn Val Thr Val Arg
1125 1130 1135
Asp Ala Thr Ser Tyr Arg Cys Gly Val Gly Pro Pro Gly Arg Ala Pro

1140 1145 1150
Arg Leu Ser Arg Pro Ile Thr Leu Asp Val Leu Tyr Ala Pro Arg Asn
1155 1160 1165
Leu Arg Leu Thr Tyr Leu Leu Glu Ser His Gly Gly Gln Leu Ala Leu
1170 1175 1180
Val Leu Cys Thr Val Asp Ser Arg Pro Pro Ala Gln Leu Ala Leu Ser
1185 1190 1195 1200
His Ala Gly Arg Leu Leu Ala Ser Ser Thr Ala Ala Ser Val Pro Asn
1205 1210 1215
Thr Leu Arg Leu Glu Leu Arg Gly Pro Gln Pro Arg Asp Glu Gly Phe
1220 1225 1230
Tyr Ser Cys Ser Ala Arg Ser Pro Leu Gly Gln Ala Asn Thr Ser Leu
1235 1240 1245
Glu Leu Arg Leu Glu Gly Val Arg Val Ile Leu Ala Pro Glu Ala Ala
1250 1255 1260
Val Pro Glu Gly Ala Pro Ile Thr Val Thr Cys Ala Asp Pro Ala Ala
1265 1270 1275 1280
His Ala Pro Thr Leu Tyr Thr Trp Tyr His Asn Gly Arg Trp Leu Gln
1285 1290 1295
Glu Gly Pro Ala Ala Ser Leu Ser Phe Leu Val Ala Thr Arg Ala His
1300 1305 1310
Ala Gly Ala Tyr Ser Cys Gln Ala Gln Asp Ala Gln Gly Thr Arg Ser
1315 1320 1325
Ser Arg Pro Ala Ala Leu Gln Val Leu Tyr Ala Pro Gln Asp Ala Val
1330 1335 1340
Leu Ser Ser Phe Arg Asp Ser Arg Ala Arg Ser Met Ala Val Ile Gln
1345 1350 1355 1360
Cys Thr Val Asp Ser Glu Pro Pro Ala Glu Leu Ala Leu Ser His Asp
1365 1370 1375
Gly Lys Val Leu Ala Thr Ser Ser Gly Val His Ser Leu Ala Ser Gly
1380 1385 1390
Thr Gly His Val Gln Val Ala Arg Asn Ala Leu Arg Leu Gln Val Gln
1395 1400 1405
Asp Val Pro Ala Gly Asp Asp Thr Tyr Val Cys Thr Ala Gln Asn Leu
1410 1415 1420
Leu Gly Ser Ile Ser Thr Ile Gly Arg Leu Gln Val Glu Gly Ala Arg
1425 1430 1435 1440
Val Val Ala Glu Pro Gly Leu Asp Val Pro Glu Gly Ala Ala Leu Asn
1445 1450 1455
Leu Ser Cys Arg Leu Leu Gly Gly Pro Gly Pro Val Gly Asn Ser Thr
1460 1465 1470
Phe Ala Trp Phe Trp Asn Asp Arg Arg Leu His Ala Glu Pro Val Pro

1475 1480 1485
Thr Leu Ala Phe Thr His Val Ala Arg Ala Gln Ala Gly Met Tyr His
1490 1495 1500
Cys Leu Ala Glu Leu Pro Thr Gly Ala Ala Ala Ser Ala Pro Val Met
1505 1510 1515 1520
Leu Arg Val Leu Tyr Pro Pro Lys Thr Pro Thr Met Met Val Phe Val
1525 1530 1535
Glu Pro Glu Gly Gly Leu Arg Gly Ile Leu Asp Cys Arg Val Asp Ser
1540 1545 1550
Glu Pro Leu Ala Ser Leu Thr Leu His Leu Gly Ser Arg Leu Val Ala
1555 1560 1565
Ser Ser Gln Pro Gln Gly Ala Pro Ala Glu Pro His Ile His Val Leu
1570 1575 1580
Ala Ser Pro Asn Ala Leu Arg Val Asp Ile Glu Ala Leu Arg Pro Ser
1585 1590 1595 1600
Asp Gln Gly Glu Tyr Ile Cys Ser Ala Ser Asn Val Leu Gly Ser Ala
1605 1610 1615
Ser Thr Ser Thr Tyr Phe Gly Val Arg Ala Leu His Arg Leu His Gln
1620 1625 1630
Phe Gln Gln Leu Leu Trp Val Leu Gly Leu Leu Val Gly Leu Leu Leu
1635 1640 1645
Leu Leu Leu Gly Leu Gly Ala Cys Tyr Thr Trp Arg Arg Arg Arg Val
1650 1655 1660
Cys Lys Gln Ser Met Gly Glu Asn Ser Val Glu Met Ala Phe Gln Lys
1665 1670 1675 1680
Glu Thr Thr Gln Gly Phe Leu Cys Gly Lys Leu Ile Asp Pro Asp Ala
1685 1690 1695
Ala Thr Cys Glu Thr Ser Thr Cys Ala Pro Pro Leu Gly
1700 1705

<210> 36
<211> 1694
<212> PRT
<213> Homo sapiens

<400> 36
Met Gly Phe Leu Pro Lys Leu Leu Leu Leu Ala Ser Phe Phe Pro Ala
1 5 10 15
Gly Gln Ala Ser Trp Gly Val Ser Ser Pro Gln Asp Val Gln Gly Val
20 25 30
Lys Gly Ser Cys Leu Leu Ile Pro Cys Ile Phe Ser Phe Pro Ala Asp
35 40 45

```
Val Glu Val Pro Asp Gly Ile Thr Ala Ile Trp Tyr Tyr Asp Tyr Ser
    50                  55                  60
Gly Gln Arg Gln Val Val Ser His Ser Ala Asp Pro Lys Leu Val Glu
65                  70                  75                  80
Ala Arg Phe Arg Gly Arg Thr Glu Phe Met Gly Asn Pro Glu His Arg
                85                  90                  95
Val Cys Asn Leu Leu Leu Lys Asp Leu Gln Pro Glu Asp Ser Gly Ser
            100                 105                 110
Tyr Asn Phe Arg Phe Glu Ile Ser Glu Val Asn Arg Trp Ser Asp Val
        115                 120                 125
Lys Gly Thr Leu Val Thr Val Thr Glu Glu Pro Arg Val Pro Thr Ile
    130                 135                 140
Ala Ser Pro Val Glu Leu Leu Glu Gly Thr Glu Val Asp Phe Asn Cys
145                 150                 155                 160
Ser Thr Pro Tyr Val Cys Leu Gln Glu Gln Val Arg Leu Gln Trp Gln
                165                 170                 175
Gly Gln Asp Pro Ala Arg Ser Val Thr Phe Asn Ser Gln Lys Phe Glu
            180                 185                 190
Pro Thr Gly Val Gly His Leu Glu Thr Leu His Met Ala Met Ser Trp
        195                 200                 205
Gln Asp His Gly Arg Ile Leu Arg Cys Gln Leu Ser Val Ala Asn His
    210                 215                 220
Arg Ala Gln Ser Glu Ile His Leu Gln Val Lys Tyr Ala Pro Lys Gly
225                 230                 235                 240
Val Lys Ile Leu Leu Ser Pro Ser Gly Arg Asn Ile Leu Pro Gly Glu
                245                 250                 255
Leu Val Thr Leu Thr Cys Gln Val Asn Ser Ser Tyr Pro Ala Val Ser
            260                 265                 270
Ser Ile Lys Trp Leu Lys Asp Gly Val Arg Leu Gln Thr Lys Thr Gly
        275                 280                 285
Val Leu His Leu Pro Gln Ala Ala Trp Ser Asp Ala Gly Val Tyr Thr
    290                 295                 300
Cys Gln Ala Glu Asn Gly Val Gly Ser Leu Val Ser Pro Pro Ile Ser
305                 310                 315                 320
Leu His Ile Phe Met Ala Glu Val Gln Val Ser Pro Ala Gly Pro Ile
                325                 330                 335
Leu Glu Asn Gln Thr Val Thr Leu Val Cys Asn Thr Pro Asn Glu Ala
            340                 345                 350
Pro Ser Asp Leu Arg Tyr Ser Trp Tyr Lys Asn His Val Leu Leu Glu
        355                 360                 365
Asp Ala His Ser His Thr Leu Arg Leu His Leu Ala Thr Arg Ala Asp
    370                 375                 380
```

```
Thr Gly Phe Tyr Phe Cys Glu Val Gln Asn Val His Gly Ser Glu Arg
385                 390                 395                 400
Ser Gly Pro Val Ser Val Val Val Asn Leu Leu Thr Ala Phe Leu Glu
                405                 410                 415
Thr Gln Ala Gly Leu Val Gly Ile Leu His Cys Ser Val Val Ser Glu
            420                 425                 430
Pro Leu Ala Thr Leu Val Leu Ser His Gly Gly His Ile Leu Ala Ser
        435                 440                 445
Thr Ser Gly Asp Ser Asp His Ser Pro Arg Phe Ser Gly Thr Ser Gly
    450                 455                 460
Pro Asn Ser Leu Arg Leu Glu Ile Arg Asp Leu Glu Glu Thr Asp Ser
465                 470                 475                 480
Gly Glu Tyr Lys Cys Ser Ala Thr Asn Ser Leu Gly Asn Ala Thr Ser
                485                 490                 495
Thr Leu Asp Phe His Ala Asn Ala Ala Arg Leu Leu Ile Ser Pro Ala
            500                 505                 510
Ala Glu Val Val Glu Gly Gln Ala Val Thr Leu Ser Cys Arg Ser Gly
        515                 520                 525
Leu Ser Pro Thr Pro Asp Ala Arg Phe Ser Trp Tyr Leu Asn Gly Ala
    530                 535                 540
Leu Leu His Glu Gly Pro Gly Ser Ser Leu Leu Leu Pro Ala Ala Ser
545                 550                 555                 560
Ser Thr Asp Ala Gly Ser Tyr His Cys Arg Ala Arg Asp Gly His Ser
                565                 570                 575
Ala Ser Gly Pro Ser Ser Pro Ala Val Leu Thr Val Leu Tyr Pro Pro
            580                 585                 590
Arg Gln Pro Thr Phe Thr Thr Arg Leu Asp Leu Asp Ala Ala Gly Ala
        595                 600                 605
Gly Ala Gly Arg Arg Gly Leu Leu Leu Cys Arg Val Asp Ser Asp Pro
    610                 615                 620
Pro Ala Arg Leu Gln Leu Leu His Lys Asp Arg Val Val Ala Thr Ser
625                 630                 635                 640
Leu Pro Ser Gly Gly Gly Cys Ser Thr Cys Gly Gly Cys Ser Pro Arg
                645                 650                 655
Met Lys Val Thr Lys Ala Pro Asn Leu Leu Arg Val Glu Ile His Asn
            660                 665                 670
Pro Leu Leu Glu Glu Glu Gly Leu Tyr Leu Cys Glu Ala Ser Asn Ala
        675                 680                 685
Leu Gly Asn Ala Ser Thr Ser Ala Thr Phe Asn Gly Gln Ala Thr Val
    690                 695                 700
Leu Ala Ile Ala Pro Ser His Thr Leu Gln Glu Gly Thr Glu Ala Asn
705                 710                 715                 720
```

```
Leu Thr Cys Asn Val Ser Arg Glu Ala Ala Gly Ser Pro Ala Asn Phe
                725                 730                 735
Ser Trp Phe Arg Asn Gly Val Leu Trp Ala Gln Gly Pro Leu Glu Thr
            740                 745                 750
Val Thr Leu Leu Pro Val Ala Arg Thr Asp Ala Ala Leu Tyr Ala Cys
        755                 760                 765
Arg Ile Leu Thr Glu Ala Gly Ala Gln Leu Ser Thr Pro Val Leu Leu
    770                 775                 780
Ser Val Leu Tyr Pro Pro Asp Arg Pro Lys Leu Ser Ala Leu Leu Asp
785                 790                 795                 800
Met Gly Gln Gly His Met Ala Leu Phe Ile Cys Thr Val Asp Ser Arg
                805                 810                 815
Pro Leu Ala Leu Leu Ala Leu Phe His Gly Glu His Leu Leu Ala Thr
            820                 825                 830
Ser Leu Gly Pro Gln Val Pro Ser His Gly Arg Phe Gln Ala Lys Ala
        835                 840                 845
Glu Ala Asn Ser Leu Lys Leu Glu Val Arg Glu Leu Gly Leu Gly Asp
    850                 855                 860
Ser Gly Ser Tyr Arg Cys Glu Ala Thr Asn Val Leu Gly Ser Ser Asn
865                 870                 875                 880
Thr Ser Leu Phe Phe Gln Val Arg Gly Ala Trp Val Gln Val Ser Pro
                885                 890                 895
Ser Pro Glu Leu Gln Glu Gly Gln Ala Val Val Leu Ser Cys Gln Val
            900                 905                 910
His Thr Gly Val Pro Glu Gly Thr Ser Tyr Arg Trp Tyr Arg Asp Gly
        915                 920                 925
Gln Pro Leu Gln Glu Ser Thr Ser Ala Thr Leu Arg Phe Ala Ala Ile
    930                 935                 940
Thr Leu Thr Gln Ala Gly Ala Tyr His Cys Gln Ala Gln Ala Pro Gly
945                 950                 955                 960
Ser Ala Thr Thr Ser Leu Ala Ala Pro Ile Ser Leu His Val Ser Tyr
                965                 970                 975
Ala Pro Arg His Val Thr Leu Thr Thr Leu Met Asp Thr Gly Pro Gly
            980                 985                 990
Arg Leu Gly Leu Leu Leu Cys Arg Val Asp Ser Asp Pro Pro Ala Gln
        995                 1000                1005
Leu Arg Leu Leu His Gly Asp Arg Leu Val Ala Ser Thr Leu Gln Gly
    1010                1015                1020
Val Gly Gly Pro Glu Gly Ser Ser Pro Arg Leu His Val Ala Val Ala
1025                1030                1035                1040
Pro Asn Thr Leu Arg Leu Glu Ile His Gly Ala Met Leu Glu Asp Glu
                1045                1050                1055
```

Gly Val Tyr Ile Cys Glu Ala Ser Asn Thr Leu Gly Gln Ala Ser Ala
1060 1065 1070
Ser Ala Asp Phe Asp Ala Gln Ala Val Asn Val Gln Val Trp Pro Gly
1075 1080 1085
Ala Thr Val Arg Glu Gly Gln Leu Val Asn Leu Thr Cys Leu Val Trp
1090 1095 1100
Thr Thr His Pro Ala Gln Leu Thr Tyr Thr Trp Tyr Gln Asp Gly Gln
1105 1110 1115 1120
Gln Arg Leu Asp Ala His Ser Ile Pro Leu Pro Asn Val Thr Val Arg
1125 1130 1135
Asp Ala Thr Ser Tyr Arg Cys Gly Val Gly Pro Pro Gly Arg Ala Pro
1140 1145 1150
Arg Leu Ser Arg Pro Ile Thr Leu Asp Val Leu Tyr Ala Pro Arg Asn
1155 1160 1165
Leu Arg Leu Thr Tyr Leu Leu Glu Ser His Gly Gly Gln Leu Ala Leu
1170 1175 1180
Val Leu Cys Thr Val Asp Ser Arg Pro Pro Ala Gln Leu Ala Leu Ser
1185 1190 1195 1200
His Ala Gly Arg Leu Leu Ala Ser Ser Thr Ala Ala Ser Val Pro Asn
1205 1210 1215
Thr Leu Arg Leu Glu Leu Arg Gly Pro Gln Pro Arg Asp Glu Gly Phe
1220 1225 1230
Tyr Ser Cys Ser Ala Arg Ser Pro Leu Gly Gln Ala Asn Thr Ser Leu
1235 1240 1245
Glu Leu Arg Leu Glu Gly Val Arg Val Ile Leu Ala Pro Glu Ala Ala
1250 1255 1260
Val Pro Glu Gly Ala Pro Ile Thr Val Thr Cys Ala Asp Pro Ala Ala
1265 1270 1275 1280
His Ala Pro Thr Leu Tyr Thr Trp Tyr His Asn Gly Arg Trp Leu Gln
1285 1290 1295
Glu Gly Pro Ala Ala Ser Leu Ser Phe Leu Val Ala Thr Arg Ala His
1300 1305 1310
Ala Gly Ala Tyr Ser Cys Gln Ala Gln Asp Ala Gln Gly Thr Arg Ser
1315 1320 1325
Ser Arg Pro Ala Ala Leu Gln Val Leu Tyr Ala Pro Gln Asp Ala Val
1330 1335 1340
Leu Ser Ser Phe Arg Asp Ser Arg Ala Arg Ser Met Ala Val Ile Gln
1345 1350 1355 1360
Cys Thr Val Asp Ser Glu Pro Pro Ala Glu Leu Ala Leu Ser His Asp
1365 1370 1375
Gly Lys Val Leu Ala Thr Ser Ser Gly Val His Ser Leu Ala Ser Gly
1380 1385 1390

Thr Gly His Val Gln Val Ala Arg Asn Ala Leu Arg Leu Gln Val Gln
1395 1400 1405
Asp Val Pro Ala Gly Asp Asp Thr Tyr Val Cys Thr Ala Gln Asn Leu
1410 1415 1420
Leu Gly Ser Ile Ser Thr Ile Gly Arg Leu Gln Val Glu Gly Ala Arg
1425 1430 1435 1440
Val Val Ala Glu Pro Gly Leu Asp Val Pro Glu Gly Ala Ala Leu Asn
1445 1450 1455
Leu Ser Cys Arg Leu Leu Gly Gly Pro Gly Pro Val Gly Asn Ser Thr
1460 1465 1470
Phe Ala Trp Phe Trp Asn Asp Arg Arg Leu His Ala Glu Pro Val Pro
1475 1480 1485
Thr Leu Ala Phe Thr His Val Ala Arg Ala Gln Ala Gly Met Tyr His
1490 1495 1500
Cys Leu Ala Glu Leu Pro Thr Gly Ala Ala Ala Ser Ala Pro Val Met
1505 1510 1515 1520
Leu Arg Val Leu Tyr Pro Pro Lys Thr Pro Thr Met Met Val Phe Val
1525 1530 1535
Glu Pro Glu Gly Gly Leu Arg Gly Ile Leu Asp Cys Arg Val Asp Ser
1540 1545 1550
Glu Pro Leu Ala Ser Leu Thr Leu His Leu Gly Ser Arg Leu Val Ala
1555 1560 1565
Ser Ser Gln Pro Gln Gly Ala Pro Ala Glu Pro His Ile His Val Leu
1570 1575 1580
Ala Ser Pro Asn Ala Leu Arg Val Asp Ile Glu Ala Leu Arg Pro Ser
1585 1590 1595 1600
Asp Gln Gly Glu Tyr Ile Cys Ser Ala Ser Asn Val Leu Gly Ser Ala
1605 1610 1615
Ser Thr Ser Thr Tyr Phe Gly Val Arg Ala Leu His Arg Leu His Gln
1620 1625 1630
Phe Gln Gln Leu Leu Trp Val Leu Gly Leu Leu Val Gly Leu Leu Leu
1635 1640 1645
Leu Leu Leu Gly Leu Gly Ala Cys Tyr Thr Trp Arg Asp Trp Val Leu
1650 1655 1660
Pro Tyr Trp Pro Leu Gln Glu Trp Arg Ala Asp Thr Asp Val Val Ser
1665 1670 1675 1680
Ile Leu Ile Pro Ala Pro Asp Ala Ser Leu Phe Met Thr Val
1685 1690

<210> 37
<211> 745
<212> PRT

<213> Homo sapiens

<400> 37

```
Met Phe Pro Leu Arg Ala Leu Trp Leu Val Trp Ala Leu Leu Gly Val
 1               5                  10                  15
Ala Gly Ser Cys Pro Glu Pro Cys Ala Cys Val Asp Lys Tyr Ala His
            20                  25                  30
Gln Phe Ala Asp Cys Ala Tyr Lys Glu Leu Arg Glu Val Pro Glu Gly
        35                  40                  45
Leu Pro Ala Asn Val Thr Thr Leu Ser Leu Ser Ala Asn Lys Ile Thr
    50                  55                  60
Val Leu Arg Arg Gly Ala Phe Ala Asp Val Thr Gln Val Thr Ser Leu
65                  70                  75                  80
Trp Leu Ala His Asn Glu Val Arg Thr Val Glu Pro Gly Ala Leu Ala
                85                  90                  95
Val Leu Ser Gln Leu Lys Asn Leu Asp Leu Ser His Asn Phe Ile Ser
            100                 105                 110
Ser Phe Pro Trp Ser Asp Leu Arg Asn Leu Ser Ala Leu Gln Leu Leu
        115                 120                 125
Lys Met Asn His Asn Arg Leu Gly Ser Leu Pro Arg Asp Ala Leu Gly
    130                 135                 140
Ala Leu Pro Asp Leu Arg Ser Leu Arg Ile Asn Asn Asn Arg Leu Arg
145                 150                 155                 160
Thr Leu Ala Pro Gly Thr Phe Asp Ala Leu Ser Ala Leu Ser His Leu
                165                 170                 175
Gln Leu Tyr His Asn Pro Phe His Cys Gly Cys Gly Leu Val Trp Leu
            180                 185                 190
Gln Ala Trp Ala Ala Ser Thr Arg Val Ser Leu Pro Glu Pro Asp Ser
        195                 200                 205
Ile Ala Cys Ala Ser Pro Pro Ala Leu Gln Gly Val Pro Val Tyr Arg
    210                 215                 220
Leu Pro Ala Leu Pro Cys Ala Pro Pro Ser Val His Leu Ser Ala Glu
225                 230                 235                 240
Pro Pro Leu Glu Ala Pro Gly Thr Pro Leu Arg Ala Gly Leu Ala Phe
                245                 250                 255
Val Leu His Cys Ile Ala Asp Gly His Pro Thr Pro Arg Leu Gln Trp
            260                 265                 270
Gln Leu Gln Ile Pro Gly Gly Thr Val Val Leu Glu Pro Pro Val Leu
        275                 280                 285
Ser Gly Glu Asp Asp Gly Val Gly Ala Glu Glu Gly Glu Gly Glu Gly
    290                 295                 300
Asp Gly Asp Leu Leu Thr Gln Thr Gln Ala Gln Thr Pro Thr Pro Ala
```

305 310 315 320
Pro Ala Trp Pro Ala Pro Pro Ala Thr Pro Arg Phe Leu Ala Leu Ala
325 330 335
Asn Gly Ser Leu Leu Val Pro Leu Leu Ser Ala Lys Glu Ala Gly Val
340 345 350
Tyr Thr Cys Arg Ala His Asn Glu Leu Gly Ala Asn Ser Thr Ser Ile
355 360 365
Arg Val Ala Val Ala Ala Thr Gly Pro Pro Lys His Ala Pro Gly Ala
370 375 380
Gly Gly Glu Pro Asp Gly Gln Ala Pro Thr Ser Glu Arg Lys Ser Thr
385 390 395 400
Ala Lys Gly Arg Gly Asn Ser Val Leu Pro Ser Lys Pro Glu Gly Lys
405 410 415
Ile Lys Gly Gln Gly Leu Ala Lys Val Ser Ile Leu Gly Glu Thr Glu
420 425 430
Thr Glu Pro Glu Glu Asp Thr Ser Glu Gly Glu Glu Ala Glu Asp Gln
435 440 445
Ile Leu Ala Asp Pro Ala Glu Glu Gln Arg Cys Gly Asn Gly Asp Pro
450 455 460
Ser Arg Tyr Val Ser Asn His Ala Phe Asn Gln Ser Ala Glu Leu Lys
465 470 475 480
Pro His Val Phe Glu Leu Gly Val Ile Ala Leu Asp Val Ala Glu Arg
485 490 495
Glu Ala Arg Val Gln Leu Thr Pro Leu Ala Ala Arg Trp Gly Pro Gly
500 505 510
Pro Gly Gly Ala Gly Gly Ala Pro Arg Pro Gly Arg Arg Pro Leu Arg
515 520 525
Leu Leu Tyr Leu Cys Pro Ala Gly Gly Gly Ala Ala Val Gln Trp Ser
530 535 540
Arg Val Glu Glu Gly Val Asn Ala Tyr Trp Phe Arg Gly Leu Arg Pro
545 550 555 560
Gly Thr Asn Tyr Ser Val Cys Leu Ala Leu Ala Gly Glu Ala Cys His
565 570 575
Val Gln Val Val Phe Ser Thr Lys Lys Glu Leu Pro Ser Leu Leu Val
580 585 590
Ile Val Ala Val Ser Val Phe Leu Leu Val Leu Ala Thr Val Pro Leu
595 600 605
Leu Gly Ala Ala Cys Cys His Leu Leu Ala Lys His Pro Gly Lys Pro
610 615 620
Tyr Arg Leu Ile Leu Arg Pro Gln Ala Pro Asp Pro Met Glu Lys Arg
625 630 635 640
Ile Ala Ala Asp Phe Asp Pro Arg Ala Ser Tyr Leu Glu Ser Glu Lys

645 650 655
Ser Tyr Pro Ala Gly Gly Glu Ala Gly Gly Glu Glu Pro Glu Asp Val
660 665 670
Gln Gly Glu Gly Leu Asp Glu Asp Ala Glu Gln Gly Asp Pro Ser Gly
675 680 685
Asp Leu Gln Arg Glu Glu Ser Leu Ala Ala Cys Ser Leu Val Glu Ser
690 695 700
Gln Ser Lys Ala Asn Gln Glu Glu Phe Glu Ala Gly Ser Glu Tyr Ser
705 710 715 720
Asp Arg Leu Pro Leu Gly Ala Glu Ala Val Asn Ile Ala Gln Glu Ile
725 730 735
Asn Gly Asn Tyr Arg Gln Thr Ala Gly
740 745

<210> 38
<211> 251
<212> PRT
<213> Homo sapiens

<400> 38
Met Ser Ala Tyr Gly Met Pro Met Tyr Lys Ser Gly Asp Leu Val Phe
1 5 10 15
Ala Lys Leu Lys Gly Tyr Ala His Trp Pro Ala Arg Ile Glu His Met
20 25 30
Thr Gln Pro Asn Arg Tyr Gln Val Phe Phe Phe Gly Thr His Glu Thr
35 40 45
Ala Phe Leu Ser Pro Lys Arg Leu Phe Pro Tyr Lys Glu Cys Lys Glu
50 55 60
Lys Phe Gly Lys Pro Asn Lys Arg Arg Gly Phe Ser Ala Gly Leu Trp
65 70 75 80
Glu Ile Glu Asn Asn Pro Thr Val Gln Ala Ser Asp Cys Pro Leu Ala
85 90 95
Ser Glu Lys Gly Ser Gly Asp Gly Pro Trp Pro Glu Pro Glu Ala Ala
100 105 110
Glu Gly Asp Glu Asp Lys Pro Thr His Ala Gly Gly Gly Gly Asp Glu
115 120 125
Leu Gly Lys Pro Asp Asp Asp Lys Pro Thr Glu Glu Glu Lys Gly Pro
130 135 140
Leu Lys Arg Ser Ala Gly Asp Pro Pro Glu Asp Ala Pro Lys Arg Pro
145 150 155 160
Lys Glu Ala Ala Pro Asp Gln Glu Glu Glu Ala Glu Ala Glu Arg Ala
165 170 175

```
Ala Glu Ala Glu Arg Ala Ala Ala Ala Ala Ala Ala Thr Ala Val Asp
            180                 185                 190
Glu Glu Ser Pro Phe Leu Val Ala Val Glu Asn Gly Ser Ala Pro Ser
        195                 200                 205
Glu Pro Gly Leu Val Cys Glu Pro Pro Gln Pro Glu Glu Glu Glu Leu
    210                 215                 220
Arg Glu Glu Glu Val Ala Asp Glu Glu Ala Ser Gln Glu Trp His Ala
225                 230                 235                 240
Glu Ala Pro Gly Gly Gly Asp Arg Asp Ser Leu
                245                 250
```

<210> 39
<211> 408
<212> PRT
<213> Homo sapiens

<400> 39

```
Phe Leu Ile Ser Asp Arg Asp Pro Gln Cys Asn Leu His Cys Ser Arg
 1               5                  10                  15
Thr Gln Pro Lys Pro Ile Cys Ala Ser Asp Gly Arg Ser Tyr Glu Ser
            20                  25                  30
Met Cys Glu Tyr Gln Arg Ala Lys Cys Arg Asp Pro Thr Leu Gly Val
        35                  40                  45
Val His Arg Gly Arg Cys Lys Asp Ala Gly Gln Ser Lys Cys Arg Leu
    50                  55                  60
Glu Arg Ala Gln Ala Leu Glu Gln Ala Lys Lys Pro Gln Glu Ala Val
65                  70                  75                  80
Phe Val Pro Glu Cys Gly Glu Asp Gly Ser Phe Thr Gln Val Gln Cys
                85                  90                  95
His Thr Tyr Thr Gly Tyr Cys Trp Cys Val Thr Pro Asp Gly Lys Pro
            100                 105                 110
Ile Ser Gly Ser Ser Val Gln Asn Lys Thr Pro Val Cys Ser Gly Ser
        115                 120                 125
Val Thr Asp Lys Pro Leu Ser Gln Gly Asn Ser Gly Arg Lys Asp Asp
    130                 135                 140
Gly Ser Lys Pro Thr Pro Thr Met Glu Thr Gln Pro Val Phe Asp Gly
145                 150                 155                 160
Asp Glu Ile Thr Ala Pro Thr Leu Trp Ile Lys His Leu Val Ile Lys
                165                 170                 175
Asp Ser Lys Leu Asn Asn Thr Asn Ile Arg Asn Ser Glu Lys Val Tyr
            180                 185                 190
Ser Cys Asp Gln Glu Arg Gln Ser Ala Leu Glu Glu Ala Gln Gln Asn
```

```
        195                 200                 205
Pro Arg Glu Gly Ile Val Ile Pro Glu Cys Ala Pro Gly Gly Leu Tyr
    210                 215                 220
Lys Pro Val Gln Cys His Gln Ser Thr Gly Tyr Cys Trp Cys Val Leu
225                 230                 235                 240
Val Asp Thr Gly Arg Pro Leu Pro Gly Thr Ser Thr Arg Tyr Val Met
                245                 250                 255
Pro Ser Cys Glu Ser Asp Ala Arg Ala Lys Thr Thr Glu Ala Asp Asp
            260                 265                 270
Pro Phe Lys Asp Arg Glu Leu Pro Gly Cys Pro Glu Gly Lys Lys Met
        275                 280                 285
Glu Phe Ile Thr Ser Leu Leu Asp Ala Leu Thr Thr Asp Met Val Gln
    290                 295                 300
Ala Ile Asn Ser Ala Ala Pro Thr Gly Gly Gly Arg Phe Ser Glu Pro
305                 310                 315                 320
Asp Pro Ser His Thr Leu Glu Glu Arg Val Val His Trp Tyr Phe Ser
                325                 330                 335
Gln Leu Asp Ser Asn Ser Ser Asn Asp Ile Asn Lys Arg Glu Met Lys
            340                 345                 350
Pro Phe Lys Arg Tyr Val Lys Lys Lys Ala Lys Pro Lys Lys Cys Ala
        355                 360                 365
Arg Arg Phe Thr Asp Tyr Cys Asp Leu Asn Lys Asp Lys Val Ile Ser
    370                 375                 380
Leu Pro Glu Leu Lys Gly Cys Leu Gly Val Ser Lys Glu Gly Gly Ser
385                 390                 395                 400
Leu Gly Ser Phe Pro Gln Ala Lys
                405
```

<210> 40
<211> 434
<212> PRT
<213> Homo sapiens

<400> 40

```
Met Ala Gly Ser Gly Pro Pro Leu Pro Thr Cys Asn Ala Glu Val Gly
 1               5                  10                  15
Trp Glu Asn Met Ala Glu Asp Gly Lys Ala Phe Leu Ile Ser Asp Arg
            20                  25                  30
Asp Pro Gln Cys Asn Leu His Cys Ser Arg Thr Gln Pro Lys Pro Ile
        35                  40                  45
Cys Ala Ser Asp Gly Arg Ser Tyr Glu Ser Met Cys Glu Tyr Gln Arg
    50                  55                  60
```

```
Ala Lys Cys Arg Asp Pro Thr Leu Gly Val Val His Arg Gly Arg Cys
65                  70                  75                  80
Lys Asp Ala Gly Gln Ser Lys Cys Arg Leu Glu Arg Ala Gln Ala Leu
                85                  90                  95
Glu Gln Ala Lys Lys Pro Gln Glu Ala Val Phe Val Pro Glu Cys Gly
            100                 105                 110
Glu Asp Gly Ser Phe Thr Gln Val Gln Cys His Thr Tyr Thr Gly Tyr
        115                 120                 125
Cys Trp Cys Val Thr Pro Asp Gly Lys Pro Ile Ser Gly Ser Ser Val
    130                 135                 140
Gln Asn Lys Thr Pro Val Cys Ser Gly Ser Val Thr Asp Lys Pro Leu
145                 150                 155                 160
Ser Gln Gly Asn Ser Gly Arg Lys Asp Asp Gly Ser Lys Pro Thr Pro
                165                 170                 175
Thr Met Glu Thr Gln Pro Val Phe Asp Gly Asp Glu Ile Thr Ala Pro
            180                 185                 190
Thr Leu Trp Ile Lys His Leu Val Ile Lys Asp Ser Lys Leu Asn Asn
        195                 200                 205
Thr Asn Ile Arg Asn Ser Glu Lys Val Tyr Ser Cys Asp Gln Glu Arg
    210                 215                 220
Gln Ser Ala Leu Glu Glu Ala Gln Gln Asn Pro Arg Glu Gly Ile Val
225                 230                 235                 240
Ile Pro Glu Cys Ala Pro Gly Gly Leu Tyr Lys Pro Val Gln Cys His
                245                 250                 255
Gln Ser Thr Gly Tyr Cys Trp Cys Val Leu Val Asp Thr Gly Arg Pro
            260                 265                 270
Leu Pro Gly Thr Ser Thr Arg Tyr Val Met Pro Ser Cys Glu Ser Asp
        275                 280                 285
Ala Arg Ala Lys Thr Thr Glu Ala Asp Asp Pro Phe Lys Asp Arg Glu
    290                 295                 300
Leu Pro Gly Cys Pro Glu Gly Lys Lys Met Glu Phe Ile Thr Ser Leu
305                 310                 315                 320
Leu Asp Ala Leu Thr Thr Asp Met Val Gln Ala Ile Asn Ser Ala Ala
                325                 330                 335
Pro Thr Gly Gly Gly Arg Phe Ser Glu Pro Asp Pro Ser His Thr Leu
            340                 345                 350
Glu Glu Arg Val Val His Trp Tyr Phe Ser Gln Leu Asp Ser Asn Ser
        355                 360                 365
Ser Asn Asp Ile Asn Lys Arg Glu Met Lys Pro Phe Lys Arg Tyr Val
    370                 375                 380
Lys Lys Lys Ala Lys Pro Lys Lys Cys Ala Arg Arg Phe Thr Asp Tyr
385                 390                 395                 400
```

```
Cys Asp Leu Asn Lys Asp Lys Val Ile Ser Leu Pro Glu Leu Lys Gly
                405                 410                 415
Cys Leu Gly Val Ser Lys Glu Gly Gly Ser Leu Gly Ser Phe Pro Gln
            420                 425                 430
Ala Lys
```

<210> 41
<211> 250
<212> PRT
<213> Homo sapiens

<400> 41

```
Met Ala Cys Trp Trp Pro Leu Leu Leu Glu Leu Trp Thr Val Met Pro
 1               5                  10                  15
Thr Trp Ala Gly Asp Glu Leu Leu Asn Ile Cys Met Asn Ala Lys His
            20                  25                  30
His Lys Arg Val Pro Ser Pro Glu Asp Lys Leu Tyr Glu Glu Cys Ile
        35                  40                  45
Pro Trp Lys Asp Asn Ala Cys Cys Thr Leu Thr Thr Ser Trp Glu Ala
    50                  55                  60
His Leu Asp Val Ser Pro Leu Tyr Asn Phe Ser Leu Phe His Cys Gly
65                  70                  75                  80
Leu Leu Met Pro Gly Cys Arg Lys His Phe Ile Gln Ala Ile Cys Phe
                85                  90                  95
Tyr Glu Cys Ser Pro Asn Leu Gly Pro Trp Ile Gln Pro Val Gly Ser
            100                 105                 110
Leu Gly Trp Glu Val Ala Pro Ser Gly Gln Gly Glu Arg Val Val Asn
        115                 120                 125
Val Pro Leu Cys Gln Glu Asp Cys Glu Glu Trp Trp Glu Asp Cys Arg
    130                 135                 140
Met Ser Tyr Thr Cys Lys Ser Asn Trp Arg Gly Gly Trp Asp Trp Ser
145                 150                 155                 160
Gln Gly Lys Asn Arg Cys Pro Lys Gly Ala Gln Cys Leu Pro Phe Ser
                165                 170                 175
His Tyr Phe Pro Thr Pro Ala Asp Leu Cys Glu Lys Thr Trp Ser Asn
            180                 185                 190
Ser Phe Lys Ala Ser Pro Glu Arg Arg Asn Ser Gly Arg Cys Leu Gln
        195                 200                 205
Lys Trp Phe Glu Pro Ala Gln Gly Asn Pro Asn Val Ala Val Ala Arg
    210                 215                 220
Leu Phe Ala Ser Ser Ala Pro Ser Trp Glu Leu Ser Tyr Thr Ile Met
```

225 230 235 240
Val Cys Ser Leu Phe Leu Pro Phe Leu Ser
245 250

<210> 42
<211> 257
<212> PRT
<213> Homo sapiens

<400> 42
Met Gly Thr Val Arg Pro Pro Arg Pro Ser Leu Leu Leu Val Ser Thr
1 5 10 15
Arg Glu Ser Cys Leu Phe Leu Leu Phe Cys Leu His Leu Gly Ala Ala
20 25 30
Cys Pro Gln Pro Cys Arg Cys Pro Asp His Ala Gly Ala Val Ala Val
35 40 45
Phe Cys Ser Leu Arg Gly Leu Gln Glu Val Pro Glu Asp Ile Pro Ala
50 55 60
Asn Thr Val Leu Leu Lys Leu Asp Ala Asn Lys Ile Ser His Leu Pro
65 70 75 80
Asp Gly Ala Phe Gln His Leu His Arg Leu Arg Glu Leu Asp Leu Ser
85 90 95
His Asn Ala Ile Glu Ala Ile Gly Ser Ala Thr Phe Ala Gly Leu Ala
100 105 110
Gly Gly Leu Arg Leu Leu Asp Leu Ser Tyr Asn Arg Ile Gln Arg Ile
115 120 125
Pro Lys Asp Ala Leu Gly Lys Leu Ser Ala Lys Ile Arg Leu Ser His
130 135 140
Asn Pro Leu His Cys Glu Cys Ala Leu Gln Glu Ala Leu Trp Glu Leu
145 150 155 160
Lys Leu Asp Pro Asp Ser Val Asp Glu Ile Ala Cys His Thr Ser Val
165 170 175
Gln Glu Glu Phe Val Gly Lys Pro Leu Val Gln Ala Leu Asp Ala Gly
180 185 190
Ala Ser Leu Cys Ser Val Pro His Arg Thr Thr Asp Val Ala Met Leu
195 200 205
Val Thr Met Phe Gly Trp Phe Ala Met Val Ile Ala Tyr Val Val Tyr
210 215 220
Tyr Val Arg His Asn Gln Glu Asp Ala Arg Arg His Leu Glu Tyr Leu
225 230 235 240
Lys Ser Leu Pro Ser Ala Pro Ala Ser Lys Asp Pro Ile Gly Pro Gly
245 250 255

Pro

<210> 43
<211> 148
<212> PRT
<213> Homo sapiens

<400> 43

```
Met Leu Gly Leu Pro Trp Lys Gly Gly Leu Ser Trp Ala Leu Leu Leu
 1               5                  10                  15
Leu Leu Leu Gly Ser Gln Ile Leu Leu Ile Tyr Ala Trp His Phe His
            20                  25                  30
Glu Gln Arg Asp Cys Asp Glu His Asn Val Met Ala Arg Tyr Leu Pro
        35                  40                  45
Ala Thr Val Glu Phe Ala Val His Thr Phe Asn Gln Gln Ser Lys Asp
    50                  55                  60
Tyr Tyr Ala Tyr Arg Leu Gly His Ile Leu Asn Ser Trp Lys Glu Gln
65                  70                  75                  80
Val Glu Ser Lys Thr Val Phe Ser Met Glu Leu Leu Leu Gly Arg Thr
                85                  90                  95
Arg Cys Gly Lys Phe Glu Asp Asp Ile Asp Asn Cys His Phe Gln Glu
            100                 105                 110
Ser Thr Glu Leu Asn Asn Val Arg Gln Asp Thr Ser Phe Pro Pro Gly
        115                 120                 125
Tyr Ser Cys Gly Cys His Met Gly Cys Gly Val Gly Thr Gly Ala Thr
    130                 135                 140
Asp Lys Glu Thr
145
```

<210> 44
<211> 355
<212> PRT
<213> Homo sapiens

<400> 44

```
Met Gly Pro Lys Asp Ser Ala Lys Cys Leu His Arg Gly Pro Gln Pro
 1               5                  10                  15
Ser His Trp Ala Ala Gly Asp Gly Pro Thr Gln Glu Arg Cys Gly Pro
            20                  25                  30
Arg Ser Leu Gly Ser Pro Val Leu Gly Leu Asp Thr Cys Arg Ala Trp
        35                  40                  45
```

```
Asp His Val Asp Gly Gln Ile Leu Gly Gln Leu Arg Pro Leu Thr Glu
    50                  55                  60
Glu Glu Glu Glu Glu Gly Ala Gly Ala Thr Leu Ser Arg Gly Pro Ala
65                  70                  75                  80
Phe Pro Gly Met Gly Ser Glu Glu Leu Arg Leu Ala Ser Phe Tyr Asp
                85                  90                  95
Trp Pro Leu Thr Ala Glu Val Pro Pro Glu Leu Leu Ala Ala Ala Gly
            100                 105                 110
Phe Phe His Thr Gly His Gln Asp Lys Val Arg Cys Phe Phe Cys Tyr
        115                 120                 125
Gly Gly Leu Gln Ser Trp Lys Arg Gly Asp Asp Pro Trp Thr Glu His
    130                 135                 140
Ala Lys Trp Phe Pro Ser Cys Gln Phe Leu Leu Arg Ser Lys Gly Arg
145                 150                 155                 160
Asp Phe Val His Ser Val Gln Glu Thr His Ser Gln Leu Leu Gly Ser
                165                 170                 175
Trp Val Ser Ala Thr Ser Pro Arg Gly Ser Gly Trp Gln Trp Gly Pro
            180                 185                 190
Ala Pro Pro Ile Ser Pro Arg Pro Asp Gly Leu Trp Leu Leu Pro Gly
        195                 200                 205
Pro Val Gly Arg Thr Gly Arg Arg Ser Pro Cys Gly Pro Leu Arg Ser
    210                 215                 220
Ser Leu Lys Val Pro Arg Ser Gln Val Gln Ala Arg Asp Pro Leu Gly
225                 230                 235                 240
Glu Gly Trp Gly Arg Gly Gly Leu Arg Asp Pro Asp Leu Pro Trp Pro
                245                 250                 255
Ile Glu Gly Gly Gly Gln Gly Val Gly Thr Phe Arg Arg Pro Val Leu
            260                 265                 270
Leu Gly Gly Val Ser Pro Ala Glu Ala Gln Arg Ala Trp Trp Val Leu
        275                 280                 285
Glu Pro Pro Gly Ala Arg Asp Val Glu Ala Gln Leu Arg Arg Leu Gln
    290                 295                 300
Glu Glu Arg Thr Cys Lys Val Cys Leu Asp Arg Ala Val Ser Ile Val
305                 310                 315                 320
Phe Val Pro Cys Gly His Leu Val Cys Ala Glu Cys Ala Pro Gly Leu
                325                 330                 335
Gln Leu Cys Pro Ile Cys Arg Ala Pro Val Arg Ser Arg Val Arg Thr
            340                 345                 350
Phe Leu Ser
        355
```

<210> 45

<211> 255
<212> PRT
<213> Homo sapiens

<400> 45

```
Met Gly Pro Lys Asp Ser Ala Lys Cys Leu His Arg Gly Pro Gln Pro
 1               5                  10                  15
Ser His Trp Ala Ala Gly Asp Gly Pro Thr Gln Glu Arg Cys Gly Pro
            20                  25                  30
Arg Ser Leu Gly Ser Pro Val Leu Gly Leu Asp Thr Cys Arg Ala Trp
        35                  40                  45
Asp His Val Asp Gly Gln Ile Leu Gly Gln Leu Arg Pro Leu Thr Glu
    50                  55                  60
Glu Glu Glu Glu Glu Gly Ala Gly Ala Thr Leu Ser Arg Gly Pro Ala
65                  70                  75                  80
Phe Pro Gly Met Gly Ser Glu Glu Leu Arg Leu Ala Ser Phe Tyr Asp
                85                  90                  95
Trp Pro Leu Thr Ala Glu Val Pro Pro Glu Leu Leu Ala Ala Ala Gly
            100                 105                 110
Phe Phe His Thr Gly His Gln Asp Lys Val Arg Cys Phe Phe Cys Tyr
        115                 120                 125
Gly Gly Leu Gln Ser Trp Lys Arg Gly Asp Asp Pro Trp Thr Glu His
    130                 135                 140
Ala Lys Trp Phe Pro Leu Ser Val Pro Ala Pro Val Lys Arg Lys Arg
145                 150                 155                 160
Leu Cys Pro Gln Cys Ala Gly Asp Ser Leu Pro Ala Ala Gly Leu Leu
                165                 170                 175
Gly Pro Val Gly Arg Thr Gly Arg Arg Ser Pro Cys Gly Pro Leu Arg
            180                 185                 190
Ser Gln Gly Cys Gly Gly Ala Ala Ala Ala Ala Ala Gly Gly Glu Asp
        195                 200                 205
Val Gln Gly Val Pro Gly Pro Arg Arg Val His Arg Leu Cys Ala Val
    210                 215                 220
Arg Pro Pro Gly Leu Cys Val Cys Pro Arg Pro Ala Ala Val Pro His
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Leu Gln Ser Pro Arg Pro Gln Pro Arg Ala His Leu Pro Val Leu
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<213> Homo sapiens

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Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30
Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45
Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60
Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80
Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95
Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110
Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125
Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140
Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160
Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175
His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190
Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205
Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220
Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240
Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
                245                 250
```

INTERNATIONAL SEARCH REPORT

PCT/US01/04703

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07K 14/17; C12N 5/10, 15/12, 15/63, 15/64

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 536/23.1, 23.5, 24.3, 24.31; 435/69.1, 71.1, 71.2, 471, 325, 252.3, 254.11, 320.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/41523 A1 (YEDA RESEARCH AND DEVELOPMENT CO., LTD.) 27 December 1996 (27/12/1996), see entire document, especially pages 7-9.	1-2, 5-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 APRIL 2001	Date of mailing of the international search report 13 JUN 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PREMA MERTZ Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

530/350; 536/23.1, 23.5, 24.3, 24.31; 435/69.1, 71.1, 71.2, 471, 325, 252.3, 254.11, 320.1

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-2, 5-9, drawn to a nucleic acid of SEQ ID NO:1 encoding a protein of SEQ ID NO:24, a vector, a host cell, a method of making the protein and the protein of SEQ ID NO:24.
Group II, claims 3-4, drawn to an antibody that binds the protein of SEQ ID NO:24.

The inventions listed as Groups I-II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
Pursuant to 37 C.F.R. § 1.475 (d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first-recited product, a nucleic acid encoding a protein of SEQ ID NO:24, a vector, a host cell, a method of making the protein of SEQ ID NO:24, and the protein of SEQ ID NO:59. Further pursuant to 37
C.F.R. § 1.475 (d), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

the polynucleotides set forth in SEQ ID NO:1-23 encoding the polypeptides set forth in SEQ ID NO:24-46.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/04703

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-2, 5-9 (SEQ ID NO:1, 24)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.